KAL 12-13-01

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=> b medline caplus lifesci embase uspatfull

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         3.53       3.68

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FILE 'BIOSIS' ENTERED AT 15:29:05 ON 15 DEC 2001
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=> s (focal adhesion kinase) or fak or pp125fak

L1          6685 (FOCAL ADHESION KINASE) OR FAK OR PP125FAK

=> s l1 and (antisens? or triplex or ribozym?)

L2           234 L1 AND (ANTISENS? OR TRIPLEX OR RIBOZYM?)

=> d history
```

(FILE 'HOME' ENTERED AT 15:28:33 ON 15 DEC 2001)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL' ENTERED AT 15:28:56 ON
15 DEC 2001

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT 15:29:05 ON 15 DEC 2001
L1 6685 S (FOCAL ADHESION KINASE) OR FAK OR PP125FAK
L2 234 S L1 AND (ANTISENS? OR TRIPLEX OR RIBOZYM?)

=> s l2 and (5()fu) or florouracil

L3 40 L2 AND (5(W) FU) OR FLOROURACIL

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4 37 DUP REM L3 (3 DUPLICATES REMOVED)

=> d l4 ibib abs tot

L4 ANSWER 1 OF 37 USPATFULL
ACCESSION NUMBER: 2001:188696 USPATFULL
TITLE: **Antisense** modulation of **focal adhesion kinase** expression
INVENTOR(S): Monia, Brett P., La Costa, CA, United States
Gaarde, William A., Carlsbad, CA, United States
Nero, Pamela S., San Diego, CA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001034329	A1	20011025
APPLICATION INFO.:	US 2001-757100	A1	20010109 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US18999, filed on 13 Jul 2000, UNKNOWN Continuation of Ser. No. US 1999-377310, filed on 19 Aug 1999, GRANTED, Pat. No. US 6133031
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kathleen A. Tyrrell, Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
LINE COUNT: 1884
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds, compositions and methods are provided for inhibiting **FAK** mediated signaling. The compositions comprise **antisense** compounds targeted to nucleic acids encoding **FAK**. Methods of using these **antisense** compounds for inhibition of **FAK** expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of **FAK** are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 2 OF 37 USPATFULL
ACCESSION NUMBER: 2001:221154 USPATFULL
TITLE: SH2 domain-containing peptides
INVENTOR(S): Stewart, Timothy A., San Francisco, CA, United States
Lu, Yanmei, Belmont, CA, United States
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States

(U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6326482	B1	20011204	
	WO 9954467		19991028	
APPLICATION INFO.:	US 1999-367206		19990809	(9)
	WO 1999-US8847		19990423	
			19990809	PCT 371 date
			19990809	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-82767	19980423 (60)
	US 1998-11329	19981222 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Davis, Katharine F
LEGAL REPRESENTATIVE: Barnes, Elizabeth M.
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 39 Drawing Figure(s); 29 Drawing Page(s)
LINE COUNT: 4794

AB The present invention relates to nucleotide sequences, including expressed sequence tags (ESTs), oligonucleotide probes, polypeptides, antagonists and agonists vectors and host cells expressing, and immunoadhesions and antibodies to PRO201, PRO308 or PRO309 polypeptides.

The invention further relates to compositions and method for the diagnosis and treatment of neoplasfic cell growth and proliferation in mammals, including humans. The invention is based in part on the identification of genes that are amplified in the genome of tumor cells.

Such gene amplification is expected to be associated with the overexpression of the gene product and contribute to tumorigenesis. Accordingly, the proteins encoded by the amplified genes are believed to be useful targets for the diagnosis and/or treatment (including prevention) of certain tumors (e.g. cancer) and may act as predictors of the prognosis of tumor treatment.

L4 ANSWER 3 OF 37 USPATFULL
ACCESSION NUMBER: 2001:36655 USPATFULL
TITLE: **Antisense** inhibition of SHP-2 expression
INVENTOR(S): Bennett, C. Frank, Carlsbad, CA, United States
Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6200807	B1	20010313	
APPLICATION INFO.:	US 1999-358683		19990721	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 2592
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antisense** compounds, compositions and methods are provided for

modulating the expression of SHP-2. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding SHP-2. Methods of using these compounds for modulation of SHP-2 expression and for treatment of diseases associated with expression of SHP-2 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 4 OF 37 USPATFULL

ACCESSION NUMBER:	2001:10735 USPATFULL
TITLE:	**Antisense** modulation of integrin-linked kinase expression
INVENTOR(S):	Bennett, C. Frank, Carlsbad, CA, United States Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S):	ISIS Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6177273	B1	20010123	
APPLICATION INFO.:	US 1999-428219		19991026	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Guzo, David
ASSISTANT EXAMINER:	McGarry, Sean
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
LINE COUNT:	2549

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of Integrin-linked kinase. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding Integrin-linked kinase. Methods of using these compounds for modulation of Integrin-linked kinase expression and for treatment of diseases associated with expression of Integrin-linked kinase are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 5 OF 37 USPATFULL

ACCESSION NUMBER:	2000:138121 USPATFULL
TITLE:	**Antisense** inhibition of **focal adhesion kinase** expression
INVENTOR(S):	Monia, Brett P., LaCosta, CA, United States Gaarde, William A., Carlsbad, CA, United States
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6133031		20001017	
APPLICATION INFO.:	US 1999-377310		19990819	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Elliott, George C.
ASSISTANT EXAMINER:	Lacourciere, Karen A
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata
NUMBER OF CLAIMS:	29
EXEMPLARY CLAIM:	1
LINE COUNT:	2280

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds, compositions and methods are provided for inhibiting **FAK** mediated signaling. The compositions comprise **antisense** compounds targeted to nucleic acids encoding **FAK**. Methods of using these **antisense** compounds for

inhibition of **FAK** expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of **FAK** are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 6 OF 37 USPATFULL

ACCESSION NUMBER:	2000:127756 USPATFULL			
TITLE:	Diagnostic apparatus utilizing radiation interaction with biological tissue			
INVENTOR(S):	Masychev, Victor, Moscow, Russian Federation			
PATENT ASSIGNEE(S):	Rosslyn Medical Limited, London, United Kingdom (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6123719		20000926	
	WO 9715226		19970501	
APPLICATION INFO.:	US 1998-65031		19980423	(9)
	WO 1996-GB2604		19961024	
			19980423	PCT 371 date
			19980423	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	GB 1995-21784		19951024	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Kamm, William E.			
LEGAL REPRESENTATIVE:	Biebel & French			
NUMBER OF CLAIMS:	44			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	45 Drawing Figure(s); 27 Drawing Page(s)			
LINE COUNT:	1181			

AB A diagnostic apparatus comprises a source (1) of probing electromagnetic radiation and means (2) for transmitting the output from the probing radiation source (1) to biological tissue (3) to be examined. The apparatus also comprises means (4, 41) for detecting probing radiation reflected from the tissue (3) and stimulated radiation resulting from excitation of the tissue (3) by the probing radiation. A processing means (5-9) responsive to the reflected and stimulated radiations to produce a signal for diagnosis of the condition of the tissue and means (15, 16) for regulating the intensity of the probing radiation including a feedback circuit (16, 17, 18) for controlling the regulating means (15) and responsive to the intensity of the probing, reflected and/or stimulated radiation are also included.

L4 ANSWER 7 OF 37 USPATFULL

ACCESSION NUMBER:	2000:102123 USPATFULL			
TITLE:	**Antisense** inhibition of PI3K p85 expression			
INVENTOR(S):	Monia, Brett P., La Costa, CA, United States Cowsert, Lex M., Carlsbad, CA, United States			
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6100090		20000808	
APPLICATION INFO.:	US 1999-344521		19990625	(9)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Elliott, George C.			
ASSISTANT EXAMINER:	Zara, Jane			

LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 2852
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of PI3K p85. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding PI3K p85. Methods of using these compounds for modulation of PI3K p85 expression and for treatment of diseases associated with expression of PI3K p85 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 8 OF 37 USPATFULL
ACCESSION NUMBER: 2000:15652 USPATFULL
TITLE: L-.beta.-dioxolane uridine analogs and methods for treating and preventing Epstein-Barr virus infections
INVENTOR(S): Chu, Chung K., Athens, GA, United States
Qu, Fucheng, Lawrenceville, NJ, United States
Cheng, Yung-Chi, Woodbridge, CT, United States
PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6022876		20000208
APPLICATION INFO.:	US 1997-954922		19971021 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-749263, filed on 15 Nov 1996, now patented, Pat. No. US 5792773, issued on 11 Aug 1998
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Crane, L. Eric
LEGAL REPRESENTATIVE: Coleman, Henry D., Sudol, R. Neil
NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1315
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the discovery that certain .beta.-L-dioxolane nucleoside analogs which contain a uracil base, and preferably, a 5-halosubstituted uracil base, exhibit unexpectedly high activity against Epstein-Barr virus (EBV), Varciella-Zoster virus (VZV) and Herpes Virus 8 (HV-8). In particular, the compounds according to the present invention show potent inhibition of the replication of the virus (viral growth) in combination with very low toxicity to the host cells (i.e., animal or human tissue). Compounds are useful for treating EBV, VZV and HV-8 infections in humans.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 9 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000393792 EMBASE
TITLE: Phase II study of vinorelbine with protracted fluorouracil infusion as a second- or third-line approach for advanced breast cancer patients previously treated with anthracyclines.
AUTHOR: Berruti A.; Sperone P.; Bottini A.; Gorzegno G.; Lorusso V.; Brunelli A.; Botta M.; Tampellini M.; Donadio M.; Mancarella S.; De Lena M.; Alquati P.; Dogliotti L.
CORPORATE SOURCE: Dr. L. Dogliotti, Oncologia Medica, Azienda Ospedaliera San

Luigi, Regione Gonzole 10, 10043 Orbassano, Italy. luigi.dogliotti@unito.it

SOURCE: Journal of Clinical Oncology, (1 Oct 2000) 18/19 (3370-3377).
Refs: 43
ISSN: 0732-183X CODEN: JCONDN

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose: To evaluate the feasibility and activity of vinorelbine in association with protracted infusional fluorouracil in patients with advanced breast cancer who were previously treated with anthracycline-containing regimens. Patients and Methods: Eighty-three consecutive patients were entered onto the study. Forty-three patients experienced treatment failure or relapse after anthracycline-based, first-line chemotherapy for advanced disease and 29 experienced treatment failure or relapse after first- and second-line approaches; 11 patients experienced progressive disease within 6 months of completion of adjuvant anthracycline therapy. Sites of involvement were as follows: liver involvement, 42 patients (50.6%); lung 24 (28.9%); bone, 49 (59.0%); and skin/lymph nodes, 21 (25.3%). Treatment consisted of vinorelbine 30 mg/m2 administered on days 1 and 15 every 28 days and fluorouracil 200 mg/m2/d given continuously over a 24-hour period. Results: Toxicity was recorded for 441 cycles. The scheme was well tolerated: grade 1/2 nausea/vomiting occurred in 13 patients (15.6%), grade 1/2 diarrhea in nine (10.8%), and grade 2/3 stomatitis in six (7.2.%). Three patients (3.6%) experienced grade 3/4 leukopenia and four (4.8%) experienced grade 2/3 anemia. Grade 2/3 neurologic toxicity was observed in three cases (3.6%), and grade 2/3 hand-foot syndrome was observed in three (3.6%). The median relative dose-intensity was 92% and 100% for vinorelbine and fluorouracil, respectively. Six patients (7.2%) attained a complete clinical response and 45 (54.2%) attained a partial response, for an overall response rate of 61.4% (95% confidence interval 50.9% to 71.9%). Twenty-one patients (25.3%) obtained disease stabilization, and 11 (13.3%) experienced disease progression. Median time to progression in responding patients was 15 months; median overall survival of the entire population was 22 months. Conclusion: Vinorelbine associated with protracted infusional **florouracil** is an active and manageable scheme in advanced breast cancer patients previously treated with anthracyclines. The response obtained is durable. (C) 2000 by American Society of Clinical Oncology.

L4 ANSWER 10 OF 37 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001028037 MEDLINE
DOCUMENT NUMBER: 20432544 PubMed ID: 10974385
TITLE: Proliferation parameters in epidermoid carcinomas of the anal canal.
AUTHOR: Wong C S; Tsang R W; Cummings B J; Fyles A W; Couture J; Brierley J D; Pintilie M
CORPORATE SOURCE: Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, 610 University Avenue, Toronro, Ontario M5G 2M9, Canada.
SOURCE: RADIOTHERAPY AND ONCOLOGY, (2000 Sep) 56 (3) 349-53.
Journal code: RAE. ISSN: 0167-8140.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001116

AB PURPOSE: In a prospective study, we assessed the proliferation parameters in primary epidermoid carcinomas of the anal canal, and results were compared with those in cervical carcinomas. METHODS: Between January 1992 and December 1996, 32 patients with primary epidermoid carcinoma of the anal canal were studied prospectively. Patients were given i.v. bromodeoxyuridine and proliferation parameters were obtained using flow cytometry. The treatment protocol consisted of radiation therapy (XRT) (24 Gy/12-3.5 week split-28 Gy/14) and concurrent 5-fluorouracil and mitomycin C. Proliferation parameters were not obtained in six patients, leaving 26 patients in the analysis. There were 16 females and ten males, with two T1, 16 T2, five T3 and three T4 lesions. Median follow-up was 3.6 years. There were 22 squamous cell and four basaloid carcinomas. Six tumors were aneuploid. RESULTS: Median values for T(s) and S-phase fraction were 7.7 h and 8.2%, respectively. The median LI was 6.8% (0.9-35.7%), and the median T(pot) was 4.1 days (0.9-30 days). There was no correlation of LI or T(pot) with gender, age, tumor stage, size or histology. Local failure was observed in five patients (T(pot)>4.1 days, n=3; LI>6.8%, n=4). Isolated regional failure or distant disease in the absence of local failure was not observed. The small number of outcome events precluded a definitive analysis of the prognostic role of LI and T(pot). Values for the proliferation parameters were similar to those in our updated study of patients with carcinoma of the uterine cervix (n=107), median LI of 6.7% and median T(pot) of 5.5 days. CONCLUSIONS: We conclude that proliferation parameters in anal carcinomas are similar to those in cervical carcinomas. Rapid tumor proliferation does not have an apparent adverse impact on outcome in anal carcinomas managed by split-course XRT with concurrent 5-**florouracil** and mitomycin C.

L4 ANSWER 11 OF 37 USPATFULL

ACCESSION NUMBER:	1999:159822 USPATFULL
TITLE:	**Antisense** inhibiton of human G-alpha-12 expression
INVENTOR(S):	Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5998206		19991207
APPLICATION INFO.:	US 1999-256496		19990223 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	LeGuyader, John L.		
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata		
NUMBER OF CLAIMS:	10		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2921		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of G-alpha-12. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding G-alpha-12. Methods of using these compounds for modulation of G-alpha-12 expression and for treatment of diseases associated with expression of G-alpha-12 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 12 OF 37 USPATFULL
ACCESSION NUMBER: 1999:142139 USPATFULL
TITLE: **Antisense** modulation of G-alpha-13 expression
INVENTOR(S): Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5981732		19991109
APPLICATION INFO.:	US 1998-205860		19981204 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Degen, Nancy
ASSISTANT EXAMINER: Epps, Janet
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 2986
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of G-alpha-13. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding G-alpha-13. Methods of using these compounds for modulation of G-alpha-13 expression and for treatment of diseases associated with expression of G-alpha-13 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 13 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95274694 EMBASE
DOCUMENT NUMBER: 1995274694
TITLE: Studies on proliposomes containing 5-**florouracil**.
AUTHOR: Yin C.H.; Liu G.J.; Zhu J.B.
CORPORATE SOURCE: Department of Pharmaceutics, China Pharmaceutical University,Nanjing 210009, China
SOURCE: Proceedings of the Controlled Release Society, (1995) -/22 (482-483).
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L4 ANSWER 14 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:525636 BIOSIS
DOCUMENT NUMBER: PREV199396139043
TITLE: Effectiveness of combined induction chemotherapy and radiotherapy in advanced nasopharyngeal carcinoma.
AUTHOR(S): Dimery, I. W. (1); Peters, L. J.; Goepfert, H.; Morrison, W. H.; Byers, R. M.; Guillory, C.; McCarthy, K.; Weber, R. S.; Hong, W. K.
CORPORATE SOURCE: (1) Hematol. Oncol. Med. Group Frenso, 7130 N. Millbrook, Suite 100, Fresno, CA 93720 USA
SOURCE: Journal of Clinical Oncology, (1993) Vol. 11, No. 10, pp. 1919-1928.
ISSN: 0732-183X.
DOCUMENT TYPE: Article

LANGUAGE: English
AB Purpose: This prospective trial was conducted with the goal of achieving an improvement in both overall and progression-free survival in previously untreated patients with stage IV nasopharyngeal carcinoma who received an induction chemotherapy regimen of **florouracil** (5-FU) and cisplatin followed by radiotherapy. Patients and Methods: From January 1985 to January 1990, 47 patients with T1-4N2-3M0 squamous cell carcinoma of the nasopharynx were treated at The University of Texas (U.S.A.) M.D. Anderson Cancer Center with two to three cycles of 5-FU (1,000 mg/m-2 continuous infusion per day times 5 days) plus cisplatin (100 mg/m-2 continuous infusion on day 1 only) followed by radiotherapy using the conventional time/dose schedule. Results: The response rate to chemotherapy was 93.2% (20.5% complete response (CR); 72.7% partial response (PR)), and the overall CR rate after radiotherapy was 86%. With a median follow-vp period of 53 months, the 2-, 4-, and 6-year survival rates were 80%, 71.6%, and 67.4%; the overall treatment failure rate was 27%. Treatment was well tolerated and without significant acute or chronic toxic effects. Conclusion: The results of this prospective study demonstrate that 5-FU plus cisplatin followed by radiotherapy can induce a durable remission in a high proportion of patients with poor-prognosis stage IV nasopharyngeal carcinoma.

L4 ANSWER 15 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 93073087 EMBASE
DOCUMENT NUMBER: 1993073087
TITLE: Thyrotropin-secreting pituitary carcinoma.
AUTHOR: Mixson A.J.; Friedman T.C.; Katz D.A.; Feuerstein I.M.; Taubenberger J.K.; Colandrea J.M.; Doppman J.L.; Oldfield E.H.; Weintraub B.D.
CORPORATE SOURCE: NIDDKD, National Institutes of Health, Building 10,Bethesda, MD 20892, United States
SOURCE: Journal of Clinical Endocrinology and Metabolism, (1993) 76/2 (529-533).
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Pituitary tumors rarely metastasize outside the central nervous system. Of the more than 100 reported TSH-secreting adenomas, we now describe the first carcinoma. A 40-yr-old woman had transsphenoidal surgery for a large TSH- secreting pituitary adenoma in 1984. She had increased thyroid hormone levels with a TSH that varied from 16-31 .mu.U/mL, and an unusually high .alpha.-subunit that ranged from 125-150 ng/mL. Because of residual tumor, she had a left craniotomy in 1985 followed by radiation. Despite these therapies, she had a residual tumor that remained stable until January 1989 when her tumor nearly doubled in size. She received radiation therapy and octreotide with marked diminution of the tumor and clinical improvement. In August 1989, she presented with leg weakness, and magnetic resonance imaging revealed a large sacral mass. A biopsy confirmed that the sacral mass was a metastasis from the pituitary tumor. Due to additional metastases in the lung, she received 5-**florouracil**, cytoxan, and adriamycin, with marked decrease in her lesions. Further substantiation of the metastatic pituitary tumor was made

when the patient returned in December 1989 with a pleural effusion containing pituitary tumor cells. Of all the reported cases of TSH-secreting adenomas, this case had the highest .alpha.-subunit portending future metastases. Furthermore, the apparent response to octreotide and response to chemotherapy are encouraging and suggest that new therapies should be explored. Finally, since TSH-secreting adenomas tend to be more invasive than other pituitary tumors, this case underscores the need for early diagnosis and aggressive treatment of these tumors.

L4 ANSWER 16 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92185766 EMBASE
DOCUMENT NUMBER: 1992185766
TITLE: [Enteral nutrition efficacy in patients with esophageal carcinoma receiving combined chemo-radiation therapy]. NUTRIZIONE ENTERALE DURANTE CHEMIO-RADIOTERAPIA NEL CARCINOMA ESOFAGEO.
AUTHOR: Cozzaglio L.; Bozzetti F.; Bidoli P.; Bonfanti G.; Riva L.; Strisciuglio A.
CORPORATE SOURCE: Oncologia Chirurgica 'A', Ist Naz per Studio/Cura dei Tumori, Via G. Venezian, 1,20133 Milano, Italy
SOURCE: Rivista Italiana di Nutrizione Parenterale ed Enterale, (1992) 10/1 (37-42).
ISSN: 0393-5582 CODEN: RINEEK
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Italian
SUMMARY LANGUAGE: English; Italian
AB In an attempt to increase the poor prognosis of patients with esophageal squamous cell carcinoma, many oncologists propose a combined chemotherapy and radiation therapy approach. In these patients drug-related dysphagia, anorexia and vomiting often lead to malnutrition. The aim of this study is to investigate the efficacy of enteral nutrition during a pre-operative combined chemoradiotherapy. We analyzed 37 malnourished patients divided into two groups: group I (CTR) patients without dysphagia and no nutritional support, group II (NE) patients with dysphagia supported by enteral feeding. Oncological therapies included 5-**florouracil** (1g/m2/day, dl-4) cisplatin (100mg/m2, dl) for two cycles associated with radiotherapy (30 Gy). We have evaluated the feasibility of enteral nutrition and its effects on the nutritional status and treatment tolerance. Tube feeding was delivered for a mean period of 33 days providing 37 Cal/kg/day and 2.1 g proteins/kg/day. Five patients stopped enteral nutrition before the end of oncological treatment because of an improvement of dysphagia. Nutritional evaluations demonstrated that during the chemoradiation therapy period, the CTR group had an impairment of body weight, total protein and albumin while there was no change in the NE group. No difference in the treatment tolerance between the two groups was found. Our study demonstrates that enteral nutrition is an easy way to prevent deterioration of nutritional status during chemoradiation therapy. Dysphagia is useful for indicating nutritional support.

L4 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:614666 CAPLUS
DOCUMENT NUMBER: 115:214666
TITLE: Local therapy of malignant brain tumor with

5FU-polymer pellets and histological study of rat brain with implantation of biodegradable CDDP-lactone polymer

AUTHOR(S): Kubo, Osami; Tajika, Yasuhiko; Ara, Tetsuaki; Nitta, Masae; Kumakura, Minoru; Yoshida, Masaru; Imasaka, Minoru; Nagai, Koji

CORPORATE SOURCE: Dep. Neurosurg., Tokyo Women's Med. Coll., Tokyo, Japan

SOURCE: Drug Delivery Syst. (1991), 6(3), 195-200
CODEN: DDSYEI; ISSN: 0913-5006

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Local therapy was carried out by slowly releasing anticancer composite to malignant brain tumors. Either ACNU pellets or 5FU (5-**florouracil**) pellets were administered at the time of the operation or under CT guidance in treating 81 cases of malignant brain tumor. From 1 to 10 pellets contg. 10-20 mg ACNU of from 1-6 pellets contg. 5-20 mg 5FU were administered. In ACNU cases, the response of the tumor tissue to local therapy was not very strong and no peripheral edemas was obsd. on CT. scan. In the 5FU pellets cases, a severe brain edema was seen in and around the pellet from the 7th to 21st days after implantation of pellet. This edema gradually improved and showed low d. only around the lesion. This is presumably due to the occurrence of leucoencephalopathy because of 5FU. Sufficient histol. studies have not yet been carried out. But in one case who was reoperation on the 10th day after pellet implantation, histol. examn. revealed marked tissue necrosis and no remaining tumor cells were seen. Thus the tissue response to 5FU is extremely strong. 5FU-pellet shows a stronger cytotoxic effect and greater degree of tissue infiltration than ACNU. Copolymers of lactic acid and valerolactone with a no.-av. mol. wt. of 1500-2600 were developed as biodegradable carriers for drug delivery. When CDDP-lactone polymer was implanted in the brain of rat, histol., the brain tissue is markedly changed. The area of necrosis and response of connective tissue were seen around the implantation site from 5th day to 20th days.

L4 ANSWER 18 OF 37 LIFESCI COPYRIGHT 2001 CSA

ACCESSION NUMBER: 90:30961 LIFESCI

TITLE: Induction, accumulation, and persistence of sister chromatid exchanges in women with breast cancer receiving cyclophosphamide, adriamycin, and 5-fluorouracil chemotherapy.

AUTHOR: Tucker, J.D.; Wyrobek, A.J.; Ashworth, L.K.; Christensen, M.L.; Burton, G.V.; Carrano, A.V.; Everson, R.B.

CORPORATE SOURCE: Lawrence Livermore Natl. Lab., Biomed. Sci. Div., P.O. Box 5507, L-452, Univ. California, Livermore, CA 94551, USA

SOURCE: CANCER RES., (1990) vol. 50, no. 16, pp. 4951-4956.

DOCUMENT TYPE: Journal

FILE SEGMENT: G; G3; X

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The induction, accumulation, and persistence of sister chromatid exchanges (SCEs) and high SCE frequency cells (HFCs) was measured in peripheral blood lymphocytes of women with breast cancer before chemotherapy and on multiple occasions during and after therapy. Chemotherapy consisted of i.v. infusion of cyclophosphamide, adriamycin, and 5-fluorouracil, administered on day 1 of each of approximately six 21-day cycles. This treatment resulted in a highly significant induction of SCEs (1.8-fold, $P < 0.0001$) and HFCs (5-fold, $P < 0.0001$) measured in samples obtained 1 week after the first therapy. Accumulation of lesions leading to SCEs was measured by comparing samples surrounding the first and last rounds of therapy and was significant for both SCEs and HFCs in most comparisons.

L4 ANSWER 19 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1991:116642 BIOSIS

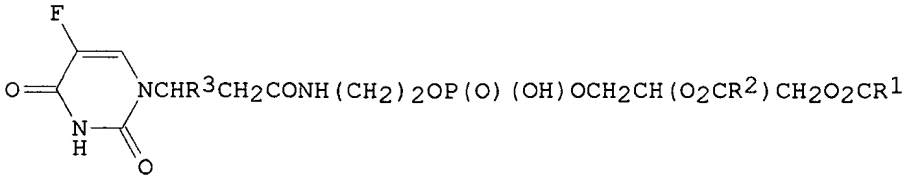
DOCUMENT NUMBER: BA91:64032
TITLE: PHASE II TRIAL OF UFT IN ADVANCED COLORECTAL AND GASTRIC CANCER.
AUTHOR(S): MALIK S T A; TALBOT D; CLARKE P I; OSBORNE R; REZNEK R; WRIGLEY P F M; SLEVIN M L
CORPORATE SOURCE: ICRF DEP. MEDICAL ONCOL., HOMERTON HOSPITAL, HOMERTON ROW, LONDON E9 6SR, UK.
SOURCE: BR J CANCER, (1990) 62 (6), 1023-1025.
CODEN: BJCAAI. ISSN: 0007-0920.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB A phase II trial of continuous oral therapy with UFT, a combination of uracil and the 5-**florouracil** analogue 1-(2-tetrahydrofuryl)-5-fluorouracil (Futraful, Ftorafur), was conducted in 40 patients with advanced colorectal cancer and 18 patients with advanced gastric cancer. Six partial responses were seen in the 36 evaluable patients with colorectal cancer (response rate 16.6%,; 95% confidence limits 6.4-32.8%), and one partial response was seen in the 16 evaluable patients with gastric cancer (response rate 6%; 95% confidence limits 0.27-30.2%). The overall toxicity of the treatment was low, and all patients were treated as outpatients. The results suggest that oral UFT has comparable activity to standard regimes of 5-fluorouracil, and because of the convenience of oral administration is a useful therapy in the management of patients with advanced colorectal cancer.

L4 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:158830 CAPLUS
DOCUMENT NUMBER: 112:158830
TITLE: 5-Fluorouracil group-containing phospholipids as anticancer agents and preparation thereof
INVENTOR(S): Nakaya, Tadao
PATENT ASSIGNEE(S): Chisso Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01226892	A2	19890911	JP 1988-54330	19880308
JP 06089008	B4	19941109		

OTHER SOURCE(S): MARPAT 112:158830
GI



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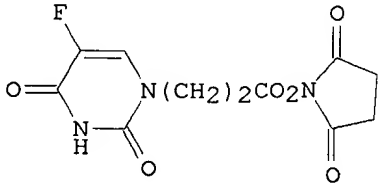


II

AB Title compds. I [R1,R2 = (un)satd. C1-30 alkyl; R3 = H, (un)satd. C1-10 alkyl], useful as anticancer agents (no data), are prepd. Treatment of 1-.beta.-carboxyethyl-5-flurouracil with N-hydroxysuccinimide in THF in the presence of DCC gave a propanoyloxysuccinimide II, which was condensed with dipalmitoylphosphatidylethanolamine in CHCl3 in the presence of Et3N to give I [R1 = R2 = Me(CH2)14, R3 = H].

L4 ANSWER 21 OF 37 USPATFULL

ACCESSION NUMBER:	89:98984 USPATFULL
TITLE:	Inhibiting growth of tumors with certain substituted phenoxy dimethyl acids, esters or salts
INVENTOR(S):	Numasaki, Yoso, Saitama, Japan Takahashi, Koichiro, Tokyo, Japan Ohata, Isao, Saitama, Japan
PATENT ASSIGNEE(S):	Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4886818		19891212
APPLICATION INFO.:	US 1988-198099		19880524 (7)
DISCLAIMER DATE:	20050719		
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1986-874547, filed on 16 Jun 1986, now patented, Pat. No. US 4758580		

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1985-140901	19850626

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Goldberg, Jerome D.
LEGAL REPRESENTATIVE:	Burgess, Ryan & Wayne
NUMBER OF CLAIMS:	4
EXEMPLARY CLAIM:	1
LINE COUNT:	584

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This disclosure describes compositions of matter useful as growth inhibitors of transplanted tumors in mammals; and this invention discloses a method of inducing the regression and/or palliation of various types of tumors in mammals and which are susceptible to treatment by certain substituted phenoxy dimethyl alkanoic acids, esters or salts, said method comprising giving to said mammals an effective amount of a compound of the following formula: ##STR1## [wherein A represents an imidazolyl group or a pyridyl group,

l represents 0 or 1,

m and n each, which may be the same or different, represents an integer of 1 to 6, and,

R represents a hydrogen atom or a lower alkyl group],

or a salt thereof; the invention also discloses a method of inhibition (or prevention) of metastasis of the various cancers.

The above formula compounds have low toxicity, and it is expected to apply various types of administration thereof such as oral administration and parenteral administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 22 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER:	89190437 EMBASE
DOCUMENT NUMBER:	1989190437

TITLE: Influence of the routes of continuous intrahepatic infusion of 5-fluorouracil on its pharmacokinetics.
AUTHOR: Didolkar M.S.; Jackson A.J.; Covell D.G.; Walker A.P.; Eddington N.D.
CORPORATE SOURCE: Surgical Oncology Program, University of Maryland Hospital, Baltimore, MD 21201, United States
SOURCE: Journal of Surgical Oncology, (1989) 41/3 (187-193). ISSN: 0022-4790 CODEN: JSONAU
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Continuous infusion chemotherapy via hepatic artery using newly available mechanical devices is frequently used to treat hepatic metastases to achieve a high concentration of 5-**florouracil** (5-FUra) in the hepatic circulation while minimizing systemic exposure. We compared four routes or intrahepatic adminstration to find out the best one in the canine model. To ascertain this date, 5-FUra (30 mg/kg) was given as a continuous infusion over a 3 hr period into either a systemic vein (femoral), portal vein, hepatic artery, or hepatic artery distal to its ligation after hepatic dearterialization. A total of eight dogs were studied. During 5-FUra infusion, concomitant blood samples were taken from the inferior vena cava and hepatic vein at 1, 2, 3, 5, 10, 15, 30, 60, 120, and 180 min. 5-FUra levels were determined in plasma by high-performance liquid chromatography. Blood flow in the portal vein and hepatic artery was measured by an electromagnetic flowmeter. The data described by a multicompartmental model, including the measured flows, had separate hepatic arterial and portal compartments with elimination from each described by linear kinetics. Mean area under the curve values in .mu.g/ml x min and the ratios of the systemic/hepatic vein areas following 5-FUra infusion via systemic, portal vein, hepatic artery, or hepatic artery after dearterialization routes were: 975/539 (R = 1.80), 939/748 (R = 1.35), 211/454 (R = 0.46), and 562/1,424 (R = 0.39). The results indicated that the administration of 5-FUra via the hepatic arterial route distal to its ligation results in the highest hepatic vein drug levels with the smallest systemic/hepatic vein exposure ratio , followed by intra-arterial route, while systemic and portal vein routes were not nearly as advantageous as the intra-arterial routes.

L4 ANSWER 23 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:162287 BIOSIS
DOCUMENT NUMBER: BA87:84388
TITLE: INTERACTION OF DEOXYURIDINE WITH FLUOROURACIL AND DIPYRIDAMOLE IN A HUMAN COLON CANCER CELL LINE.
AUTHOR(S): GREM J L; MULCAHY R T; MILLER E M; ALLEGRA C J; FISCHER P H
CORPORATE SOURCE: INVESTIGATIONAL DRUG BRANCH, CANCER THERAPY EVALUATION PROGRAM, DIV. CANCER TREATMENT, NATL. CANCER INST., EXECUTIVE PLAZA NORTH, ROOM 731, BETHESDA, MD. 20892.
SOURCE: BIOCHEM PHARMACOL, (1989) 38 (1), 51-60. CODEN: BCPCA6. ISSN: 0006-2952.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB We have reported previously that dipyridamole increases the toxicity of 5-fluorouracil and alters fluorouracil metabolism in HCT 116 cells,

producing a selective increase in fluorodeoxyuridine monophosphate (FdUMP) levels by blocking the efflux of fluorodeoxyuridine. Dipyridamole also blocks deoxyuridine efflux and prolongs the intracellular half-life of deoxyuridine monophosphate (dUMP). The significance of the effect of dipyridamole on FdUMP and dUMP levels was explored further. In cell growth experiments, 1-50 .mu.M deoxyuridine enhanced the cytotoxicity of 5 .mu.M fluorouracil in a dose-dependent manner, and .gtoreq. 10 .mu.M deoxyuridine increased the augmentation of fluorouracil toxicity produced by 0.5 .mu.M dipyridamole. The effect of deoxyuridine on [6-3H]fluorouracil metabolism was studied. After 4 hr, 25 .mu.M deoxyuridine increased the amount of [3H]FdUMP formed 2- to 4-fold relative to that of **florouracil** .+-. dipyridamole alone. The mechanism by which deoxyuridine increased FdUMP was examined by measuring the distribution of [2-3H]deoxyuridine metabolites following exposure of 25 .mu.M deoxyuridine .+-. 5 .mu.M fluorouracil. Tritium appeared in the FdUMP peak at 4 and 24 hr in cells exposed to fluorouracil and deoxyuridine, indicating that [3H]deoxyribose was transferred to fluorouracil. A large buildup of [3H]dUMP was seen in cells exposed to fluorouracil plux deoxyuridine for 4 and 24 hr compared to exposure to [3H]deoxyuridine alone, suggesting that dUMP may also inhibit catabolism of FdUMP. Since the increased FdUMP levels produced by dipyridamole did not appear to correlate with further depletion of thymidine triphosphate pools, the incorporation of [3H]fluorouracil metabolites into nucleic acids was monitored by cesium sulfate density centrifugation. Fluorouracil-RNA increased as a function of time (1, 2 and 13 pmol/106 cells after 4, 8 and 24 hr), but fluorouracil-DNA was detected only after 24 hr (0.5 pmol/106 cells). Dipyridamole however, did not appear to alter the pattern of incorporation of fluorouracil into either RNA or DNA. Perturbations of endogenous dUMP levels by fluorouracil and dipyridamole were then studied. In cells exposed to fluorouracil alone, dUMP pools were unchanged from control at 2 hr, but they had increased 9-fold by 4 hr (3362 pmol/106 cells). Simultaneous exposure to fluorouracil and dipyridamole resulted in a 1.5-fold (566 pmol/106 cells) and 13.6-fold (5049 pmol/106 cells) increase over control dUMP levels after 2 and 4 hr respectively. The dUMP pools continued to enlarge through 24 hr. The effect of fluorouracil on DNA fragility was examined. In cells prelabeled with [14C]thymidine, there was no evidence of single-strand breaks in high molecular weight DNA after 4 or 24 hr of exposure to fluorouracil alone or with dipyridamole as measured by alkaline elution. In contrast, fluorouracil produced alkaline labile sites in newly synthesized DNA. Alkaline labile sites were also produced by exposure to dipyridamole. Concomitant exposure to FUra with dipyridamole and/or deoxyuridine resulted in a striking increase in the alkaline labile sites in DNA. These results suggest that effects on deoxyuridine metabolism may be important components of the interaction between fluorouracil and dipyridamole.

L4 ANSWER 24 OF 37 USPATFULL

ACCESSION NUMBER:	88:45664 USPATFULL
TITLE:	Inhibiting growth of tumors with certain substituted phenoxy dimethyl alkanoic acids, esters or salts
INVENTOR(S):	Numasaki, Yoso, Saitama, Japan Takahashi, Koichiro, Tokyo, Japan Ohata, Isao, Saitama, Japan
PATENT ASSIGNEE(S):	Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 4758580 19880719
APPLICATION INFO.: US 1986-874547 19860616 (6)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1985-140901	19850626

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Goldberg, Jerome D.
LEGAL REPRESENTATIVE: Burgess, Ryan & Wayne
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 592
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This disclosure describes compositions of matter useful as growth inhibitors of transplanted tumors in mammals: and this invention discloses a method of inducing the regression and/or palliation of various types of tumors in mammals (mammary cancer, liver cancer, skin cancer, etc.), said method comprising giving to said mammals an effective amount of a compound of the following formula: ##STR1## [wherein A represents an imidazolyl group or a pyridyl group, l represents 0 or 1, m and n each, which may be the same of different, represents an integer of 1 to 6, and, R represents a hydrogen atom or a lower alkyl group], or a salt thereof; the invention also discloses a method of inhibition (or prevention) of metastasis of the various cancers.

The above formula compounds have low toxicity, and it is expected to apply various types of administration thereof such as oral administration and parenteral administration. In particular, it is expected that the compounds are useful as new type of medical (anti-cancer) compounds which can be administered orally.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 25 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:313 CAPLUS
DOCUMENT NUMBER: 108:313
TITLE: Antitumor and relevant pharmacological effects of pachyman
AUTHOR(S): Chen, Dingnan; Fan, Yijun; Zhou, Jun; Liang, Zichao
CORPORATE SOURCE: Guangxi Inst. Chin. Mater. Med., Nanning, Peop. Rep. China
SOURCE: Zhongyao Tongbao (1987), 12(9), 553-5
CODEN: CYTPDT; ISSN: 0254-0029
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB I.p. injection of pachyman, the polysaccharide of Poria cocos, had antitumor effect in mice transplanted with S180 tumor cells but did not potentiate the effect of antitumor agents (5-**florouracil**, cyclophosphamide, etc). At high doses, pachyman inhibited body wt. gain in mice. It promoted the recovery of cyclophosphamide-induced decreases in white blood cells of rats and increased the phagocytic activity of macrophages in mice treated with sheep red cells.

L4 ANSWER 26 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 87053610 EMBASE
DOCUMENT NUMBER: 1987053610
TITLE: Alteration of fluorouracil metabolism in human colon cancer cells by dipyridamole with a selective increase in fluorodeoxyuridine monophosphate levels.
AUTHOR: Grem J.L.; Fischer P.H.
CORPORATE SOURCE: Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, WI 53792, United States
SOURCE: Cancer Research, (1986) 46/12 I (6191-6199).

CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
030 Pharmacology
LANGUAGE: English
AB The nucleoside transport inhibitor dipyridamole can increase the cytotoxicity of 5-fluorouracil in a human colon cancer cell line (HCT 116) without affecting the total amount of fluorouracil incorporated into the acid soluble and insoluble fractions (J.L. Grem and P.H. Fischer, Cancer Res., 45: 2967-2972, 1985). We now report that dipyridamole altered the pattern of fluorouracil metabolism and provided a selective increase in intracellular fluorodeoxyuridine monophosphate (FdUMP) levels. At 2 and 4 h after exposure to fluorouracil and dipyridamole, FdUMP levels were approximately 5-fold higher in the presence of dipyridamole. The ratio of FdUMP to fluorouridine triphosphate at 4 h was substantially increased in the presence of dipyridamole (0.4 .+-. 0.05) compared to fluorouracil alone (0.08 .+-. 0.03). In cells preloaded with fluorodeoxyuridine (FdUrd), dipyridamole potently inhibited the efflux of FdUrd, leading to an increased retention of intracellular FdUMP. One h following removal of [6-3H]FdUrd, the FdUMP levels were increased 8-fold in the presence of dipyridamole, and the half-life of intracellular FdUMP was increased from 24 to 78 min. We have previously shown that the addition of sufficient thymidine (25 .mu.M) can prevent the augmentation of fluorouracil toxicity produced by dipyridamole. In these studies, the addition of 25 .mu.M thymidine reduced the FdUMP levels to less than half of those measured in the presence of fluorouracil plus dipyridamole for the first 8 h of exposure, and reduced the FdUMP levels to 6% of the FdUMP levels seen with fluorouracil and dipyridamole after 24 h of exposure. Thymidine prevented the enhanced intracellular retention of FdUMP produced by dipyridamole in cells preloaded with FdUrd. In addition, thymidine inhibited the accumulation of FdUMP in cells exposed to FdUrd. In cancer cells which significantly catabolize FdUMP, the ability of dipyridamole to block the efflux of FdUrd may provide an effective means of selectively increasing FdUMP levels and enhancing the toxicity of **florouracil**. Furthermore, dipyridamole blocked the efflux of deoxyuridine and prolonged the intracellular half-life of deoxyuridine monophosphate. In cells prelabeled with [2'-3H]dUrd, transfer of tritium to FdUrd and FdUMP occurred in cells exposed to fluorouracil and dipyridamole. These data suggest that blockade of nucleoside efflux can enhance the availability of deoxyribose-1-phosphate donors for the synthesis of FdUrd. Thus, dipyridamole's ability to inhibit nucleoside transport can perturb the metabolism of a nucleobase, fluorouracil.

L4 ANSWER 27 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1985:263374 BIOSIS
DOCUMENT NUMBER: BA79:43370
TITLE: MANNICH BASE DERIVATIVES OF THROPHYLLINE AND 5 FLUOROURACIL
SYNTHESES PROPERTIES AND TOPICAL DELIVERY CHARACTERISTICS.
AUTHOR(S): SLOAN K B; KOCH S A M; SIVER K G
CORPORATE SOURCE: COLLEGE PHARMACY, UNIV. FLORIDA, GAINESVILLE, FL 32610, USA.
SOURCE: INT J PHARM (AMST), (1984) 21 (3), 251-264.
CODEN: IJPHDE. ISSN: 0378-5173.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Mannich base prodrugs of theophylline and 5-fluorouracil [1,3-bis(4'-morpholinyl)methyl-5-**florouracil**,

7-(dimethylamino)methyltheophylline, 7-(diethylamino)methyltheophylline, 7-(dipropylamino)methyltheophylline, 7-(4'-morpholinyl)methyltheophylline and 7-(pyrrolidyl)methyltheophylline] were prepared and tested for their ability to deliver their parent drugs through hairless mouse skin. The Mannich base derivatives were more effective than the previously described N-acyloxyalkyl derivatives. In the case of theophylline, the Mannich base derivative was as effective as the previously described N-hydroxymethyl derivative. All of the Mannich bases reverted to their parent compounds in water, but some were relatively stable in aprotic solvents such as isopropyl myristate which was therefore used as a vehicle for the diffusion experiments with the prodrugs.

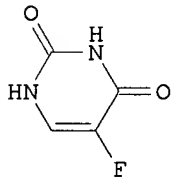
L4 ANSWER 28 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82194995 EMBASE
DOCUMENT NUMBER: 1982194995
TITLE: Combination chemotherapy (vincristine, Adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma.
AUTHOR: Evans A.E.; Land V.J.; Newton W.A.; et al.
CORPORATE SOURCE: Child. Cancer Study Group Oper. Off., Los Angeles, CA 90031, United States
SOURCE: Cancer, (1982) 50/5 (821-826).
CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
007 Pediatrics and Pediatric Surgery
048 Gastroenterology
052 Toxicology
LANGUAGE: English
AB Members of Childrens Cancer Study Group and the Pediatric Division of the Southwest Oncology Group conducted a study of chemotherapy for children with malignant liver tumors. All patients received vincristine, cyclophosphamide, Adriamycin and 5-**florouracil** in 6 weekly cycles for one year. Surgical resection and irradiation were employed when indicated. Between January 1976 and August 1978, 62 patients were entered on study; one was rejected for a protocol error, and ten had inadequate trials of chemotherapy, dying within one month of entry. The median time on study for all patients was 12 months. Twenty-four patients had no measurable disease following surgical treatment and chemotherapy was employed as adjuvant treatment; 20/24 (83%) remain relapse-free from 8-42+ months, (median, 30 months). In 27 patients, residual measurable disease was available to determine the response to chemotherapy. The response rate was 12/27 (44%), lasting 3-45 months (median, 18 months). The median follow-up of all survivors is 30 months. Hematologic toxicity was significant, particularly during initial courses of chemotherapy; 28/57 patients developed severe toxicity which was fatal in three. The results from the current study were compared to those from a previous one initiated in 1972, in which actinomycin D, vincristine, and cyclophosphamide were given in sequence, one during each month for one year. Although the population of the two studies was not identical, there was a difference in the response rates (P = 0.02), relapse-free interval (P = 0.008), and survival (P = 0.003). The most striking improvement was seen in the patients with Group I disease, there were 7/11 relapses in the first study and 1/16 in the current one.

L4 ANSWER 29 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1980:225529 BIOSIS
DOCUMENT NUMBER: BA70:18025
TITLE: COMBINED CHEMO THERAPY AND RADIO THERAPY FOR LOCALLY ADVANCED BREAST CANCER.
AUTHOR(S): RUBENS R D; SEXTON S; TONG D; WINTER P J; KNIGHT R K; HAYWARD J L
CORPORATE SOURCE: BREAST UNIT, GUYS HOSP., LONDON SE1 9RT, ENGL., UK.
SOURCE: EUR J CANCER, (1980) 16 (3), 351-356.
CODEN: EJCAAH. ISSN: 0014-2964.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB To test the feasibility of combining radiotherapy and chemotherapy as the primary management of locally advanced breast cancer, 24 patients were allocated to receive 4 courses of adriamycin and vincristine (AV) followed by radiotherapy, followed by 8 courses of cyclophosphamide, methotrexate and 5-**florouracil** (CMF) (group A), or radiotherapy followed by 4 courses of AV followed by 8 courses of CMF (group B). The objective regression rate after AV and radiotherapy was 10/12 (83%) in group A and 11/12 (92%) in group B, but the subsequent relapse rate was high, being 6/12 (50%) in group A and 7/12 (58%) in group B. The pattern of relapse, duration of objective regressions and survival in groups A and B were the same. No serious adverse side effects arose from combining chemotherapy and radiotherapy in either group. In a retrospective comparison of groups A and B with patients treated previously by radiotherapy alone, the median duration of response in this series of 33 mo. was significantly longer than in patients treated by radiotherapy alone (10.5 mo.); P .ltoreq. 0.001. Although the survival experience of the combined groups A and B (median 36 mo.) was higher than that in the previous series (25 mo.), this difference is not statistically significant. While these retrospective comparisons give rise to optimism that combining radiotherapy and chemotherapy may be helpful in the treatment of locally advanced breast cancer, prospective randomized controlled trials are now necessary to determine whether a true improvement in results can be achieved by this approach.

L4 ANSWER 30 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:140447 CAPLUS
DOCUMENT NUMBER: 92:140447
TITLE: Cell surface alterations associated with exposure of leukemia L1210 cells to fluorouracil
AUTHOR(S): Kessel, David
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Cancer Res. (1980), 40(2), 322-4
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Exposure of murine leukemia L1210 cells to graded doses of 5-fluorouracil (I) [51-21-8] for 24 h led to a progressive increase in cell surface hydrophobicity, inhibition of cell division, and an increased cell vol. Among the effects assocd. with I treatment were inhibition of thymidylate

synthetase [9031-61-2], decreased incorporation of leucine [61-90-5] into glycoprotein, and an apparently increased incorporation of thymidine [50-89-5] into DNA and of glucosamine [3416-24-8] into glycoprotein. The latter effects are apparently caused by depleted metabolite pools. Short-term treatment of L1210 cells with the drug altered only levels of thymidylate synthetase. Cell surface changes therefore appear to be related to long-term effects of I assocd. with impaired synthesis of membrane glycoprotein.

L4 ANSWER 31 OF 37 MEDLINE
ACCESSION NUMBER: 81023168 MEDLINE
DOCUMENT NUMBER: 81023168 PubMed ID: 7418311
TITLE: Extravasation of chemotherapeutic agents.
AUTHOR: Blair W F; Kilpatrick W C Jr; Saiki J H; Atler E J
SOURCE: CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1980 Sep) (151) 228-30.
Journal code: DFY; 0075674. ISSN: 0009-921X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198012
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19801218

AB The clinical course of extravasation of chemotherapeutic agents is best described for Adriamycin. The course is often one of painful erythema, gradual extensive ulceration, and finally permanent impairment of an extremity. Other chemotherapeutic agents, singly or in combination, may behave in a similar manner. Our experience with mtomycin and 5-**florouracil** suggests that they will produce a relatively severe ulceration. The efficacy of local measures of treatment after extravasation is not estabished. As soon as possible, consultation with a vascular surgeon and wide excision of areas of necrosis are advisable.

L4 ANSWER 32 OF 37 MEDLINE
ACCESSION NUMBER: 81023663 MEDLINE
DOCUMENT NUMBER: 81023663 PubMed ID: 7418570
TITLE: Combined treatment of patients with lung carcinoma. (Preliminary results assembled in international cooperative investigation).
AUTHOR: Virsik K; Gavalcova E; Badalik L; Szalmova S; Kandracova Z
SOURCE: CZECHOSLOVAK MEDICINE, (1980) 3 (2) 144-50.
Journal code: D91; 7805372. ISSN: 0139-9179.
PUB. COUNTRY: Czechoslovakia
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198012
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19980206
Entered Medline: 19801216

AB The authors submit information on the preliminary results of combined treatment of patients with carcinoma of the lungs (epidermoid, adenocarcinoma, large-cell and combined carcinoma). The patients were classified, consistents with the protocol of the study, into two basic groups, each of which was sub-divided at random into two sub-groups. In the first group of 25 patients 9 were subjected to preoperative radiotherapy--2 000 rad (Co60) and 16 patients were operated without previous radiotherapy. The second group was formed by 41 patients incl. 21 who were treated by radical Co60 therapy and 20 patients who in addition

to Co60 therapy were given the cytostatic preparation Methotrexate and 5-**Florouracil**. The submitted work is part of an international cooperative study within the framework of the Council of Mutual Economic Assistance which was started in 1976 and the enlistment of patients will be completed in 1980.

L4 ANSWER 33 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80169847 EMBASE
DOCUMENT NUMBER: 1980169847
TITLE: Morphological study of cleft palate development in 5-fluorouracil-treated hamster fetuses.
AUTHOR: Shah R.M.; Wong D.T.W.
CORPORATE SOURCE: Dept. Oral Biol., Fac. Dent., Univ. British Columbia, Vancouver, Canada
SOURCE: Journal of Embryology and Experimental Morphology, (1980) VOL.57/- (119-128).
CODEN: JEEMAF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
021 Developmental Biology and Teratology
001 Anatomy, Anthropology, Embryology and Histology
030 Pharmacology
016 Cancer
LANGUAGE: English
AB Morphogenesis of palate was studied in normal and 5-fluorouracil-treated hamster fetuses. The results showed that normal palatal development was completed between days 12 and 13 of gestation. In 5-**florouracil** -assaulted palate the reorientation of shelves from a vertical to horizontal plane was delayed. Crown-rump length, gestational age and fetal
weight were reliable predictors of the stages of normal palatal development, whereas the morphological rating system was not. Following 5-fluorouracil treatment, however, crown-rump length, weight and morphological rating were poor indicators of the stage of palatal development.

L4 ANSWER 34 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1979:109996 CAPLUS
DOCUMENT NUMBER: 90:109996
TITLE: Therapeutic agents for treatment of uterus cancer
INVENTOR(S): Nagai, Tsuneji; Machida, Yoshiharu; Masuda, Hiroshi; Fujiyama, Norimasa; Ito, Susumu; Iwata, Masanori
PATENT ASSIGNEE(S): Teijin Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 53130421	A2	19781114	JP 1977-44149	19770419
JP 56047886	B4	19811112		

AB Sustained-release therapeutic agents for treatment of uterus cancer (for uterine application) comprise hydroxypropyl cellulose [9004-64-2] and polyacrylic acid [9003-01-4] or its salts in addn. to active ingredients such as **florouracil**, cyclophosphamide, mitomycin c, and bleomycin-HCl [67763-87-5]. For example, tablets (2 mm thickness, 13 mm diam.) were prepd. contg. hydroxypropyl cellulose 0.9, polyacrylic acid 1.8, and bleomycin-HCl 300 g. The prepns. can be placed in the cervix uteri.

L4 ANSWER 35 OF 37 MEDLINE
ACCESSION NUMBER: 78045698 MEDLINE

DOCUMENT NUMBER: 78045698 PubMed ID: 924840
TITLE: Neurotoxicosis associated with use of 5-**florouracil**
.
AUTHOR: Henness A M; Theilen G H; Madewell B R; Crow S E
SOURCE: JOURNAL OF THE AMERICAN VETERINARY MEDICAL ASSOCIATION, (1977 Oct 15) 171 (8) 692.
Journal code: HAV; 7503067. ISSN: 0003-1488.
PUB. COUNTRY: United States
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197801
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780127

L4 ANSWER 36 OF 37 USPATFULL
ACCESSION NUMBER: 75:68603 USPATFULL
TITLE: Process for producing cyclic-3,5-cytidylic acid by fermentation
INVENTOR(S): Ishiyama, Jiro, Noda, Japan
Yokotsuka, Tamotsu, Nagareyama, Japan
PATENT ASSIGNEE(S): Kikkoman Shoyu Co., Ltd., Noda, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3926725		19751216
APPLICATION INFO.:	US 1974-477456		19740607 (5)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1973-U63918	19730608

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Tanenholtz, Alvin E.
LEGAL REPRESENTATIVE: Schuyler, Birch, Swindler, McKie & Beckett
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1157
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Cyclic-3',5'-cytidylic acid (CCMP) is obtained by culturing in a medium a microorganism belonging to the genus Corynebacterium, Arthrobacter or Microbacterium and having an ability of producing cyclic-3',5'-cytidylic acid.

The CCMP is important as a reagent for hormone mediator and the like in the field of biochemistry.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 37 OF 37 MEDLINE
ACCESSION NUMBER: 72193871 MEDLINE
DOCUMENT NUMBER: 72193871 PubMed ID: 5063951
TITLE: Therapeutic effects of 5-**florouracil** ointment on various skin diseases.
AUTHOR: Yamamoto K; Sasaki S
SOURCE: GAN NO RINSHO. JAPANESE JOURNAL OF CANCER CLINICS, (1972 Mar) 18 (3) 214-8.
Journal code: KIF; 1257753. ISSN: 0021-4949.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197208

ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19720801

=> d history

(FILE 'HOME' ENTERED AT 15:28:33 ON 15 DEC 2001)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL' ENTERED AT 15:28:56 ON
15 DEC 2001

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT
15:29:05 ON 15 DEC 2001
L1 6685 S (FOCAL ADHESION KINASE) OR FAK OR PP125FAK
L2 234 S L1 AND (ANTISENS? OR TRIPLEX OR RIBOZYM?)
L3 40 S L2 AND (5()FU) OR FLOROURACIL
L4 37 DUP REM L3 (3 DUPLICATES REMOVED)

=> d l4 ibib kwic tot

L4 ANSWER 1 OF 37 USPATFULL
ACCESSION NUMBER: 2001:188696 USPATFULL
TITLE: **Antisense** modulation of **focal adhesion kinase** expression
INVENTOR(S): Monia, Brett P., La Costa, CA, United States
Gaarde, William A., Carlsbad, CA, United States
Nero, Pamela S., San Diego, CA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001034329	A1	20011025
APPLICATION INFO.:	US 2001-757100	A1	20010109 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US18999, filed on 13 Jul 2000, UNKNOWN Continuation of Ser. No. US 1999-377310, filed on 19 Aug 1999, GRANTED, Pat. No. US 6133031
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kathleen A. Tyrrell, Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
LINE COUNT: 1884
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Antisense** modulation of **focal adhesion kinase** expression
AB Compounds, compositions and methods are provided for inhibiting **FAK** mediated signaling. The compositions comprise **antisense** compounds targeted to nucleic acids encoding **FAK**. Methods of using these **antisense** compounds for inhibition of **FAK** expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of **FAK** are provided.
SUMM [0002] This invention relates to compositions and methods for modulating expression of the human **focal adhesion kinase** (**FAK**) gene, which encodes a signaling protein involved in growth factor response and cell migration and is implicated in disease. This invention is also directed to methods for inhibiting **FAK**-mediated signal transduction; these methods can be used

diagnostically or therapeutically. Furthermore, this invention is directed to treatment of conditions associated with expression of the human **FAK** gene.

SUMM . . . be induced by both integrin receptor-mediated signals (haptotaxis migration) and/or soluble growth factor-mediated signals (chemotaxis migration). Integrin receptor engagement activates **focal adhesion kinase** (**FAK**, also **pp125FAK**), a non-receptor protein-tyrosine kinase localized to cell substratum-extracellular matrix (ECM) contact sites that function as part of a cytoskeletal-associated network of signaling proteins (Schlaepfer, D. D., et al., Prog. Diophys. Mol. Biol., 1999, 71, 435-478). In adherent cells, **FAK** is often associated with integrins at focal adhesions (Schaller, M. D., et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 5192-5196). Numerous other signaling proteins, including other protein tyrosine kinases are associated with **FAK** at these regions. Phosphorylation of **FAK** results in activation of the mitogen-activated protein kinase pathway. In addition, **FAK** regulates activation of phosphatidylinositol 3'-kinase which may serve to prevent apoptosis. **FAK** has also been shown to be required for internalization of bacteria mediated by invasin (Alrutz, M. A. and Isberg, R.. . .

SUMM [0005] Overexpression of **FAK** is involved in cancer progression. High levels of **FAK** correlates with invasiveness and metastatic potential in colon tumors (Weiner, T. M., et al., Lancet, 1993, 342, 1024-1025), breast tumors. . .

SUMM [0006] **FAK**'s role in cell migration has led to the speculation that it may be relevant in other diseases such as embryonic. . .

SUMM [0007] There is a lack of specific inhibitors of **FAK**. **Antisense** approaches have been a means by which the function of **FAK** has been investigated. Lou, J. et al. (J. Orthopaedic Res., 1997, 15, 911-918) used an adenoviral based vector to express **antisense FAK** RNA to show that **FAK** is involved in wound healing in tendons. Another **antisense** **FAK** expression vector containing 400 bp of complementary sequence was used to study the interaction of type I collagen and ?2?1. . .

SUMM [0008] **Antisense** oligonucleotides have been used in several studies. Tanaka, S. et al. (J. Cell. Biochem., 1995, 58, 424-435) disclose two **antisense** phosphorothioate oligonucleotides targeted to the start site of mouse **FAK**. Xu, L. -H., et al. (Cell Growth Diff., 1996, 7, 413-418) disclose two **antisense** phosphorothioate oligonucleotides targeted within the coding region of human **FAK**. They also show that **FAK antisense** treatment could induce apoptosis in tumor cells. Sonoda, Y., et al. (Biochem. Biophys. Res. Comm., 1997, 241, 769-774) also demonstrated a role for **FAK** in apoptosis using **antisense** phosphorothioate oligonucleotides targeted to the start site and within the coding region of human **FAK**. Shibata, K., et al. (Cancer Res., 1998, 58, 900-903) disclose **antisense** phosphorothioate oligonucleotides targeted to the start site and coding region of human **FAK**. Narase, K., et al. (Oncogene, 1998, 17, 455-463) disclose an **antisense** phosphorothioate oligonucleotide targeted to the start site of human **FAK**.

SUMM [0009] There remains a long-felt need for improved compositions and methods for inhibiting **FAK** gene expression.

SUMM [0010] The present invention provides **antisense** compounds which are targeted to nucleic acids encoding **focal adhesion kinase** expression (**FAK**) and are capable of modulating **FAK** mediated signaling. The present invention also provides chimeric oligonucleotides targeted to nucleic acids encoding human **FAK**. The **antisense** compounds of the invention are believed to be useful both diagnostically and therapeutically, and are believed to be particularly useful. . .

SUMM [0011] The present invention also comprises methods of modulating **FAK** mediated signaling, in cells and tissues, using the **antisense** compounds of the invention. Methods of inhibiting **FAK** expression are provided; these methods are believed to be useful both therapeutically and diagnostically. These methods are also useful as tools, for example, for detecting and determining the role of **FAK** in various cell functions and physiological processes and conditions and for diagnosing conditions associated with expression of **FAK**.

SUMM . . . cancers, including those of the colon, breast and mouth. These methods are believed to be useful, for example, in diagnosing **FAK**-associated disease progression. These methods employ the **antisense** compounds of the invention. These methods are believed to be useful both therapeutically, including prophylactically, and as clinical research and. . .

SUMM [0013] **FAK** plays important roles in integrin-mediated signal transduction. Overexpression of **FAK** is associated with tumor progression and metastatic potential. As such, this protein represents an attractive target for treatment of such diseases. In particular, modulation of the expression of **FAK** may be useful for the treatment of diseases such as colon cancer, breast cancer and cancer of the mouth.

SUMM [0014] The present invention employs **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding **FAK**, ultimately modulating the amount of **FAK** produced. This is accomplished by providing oligonucleotides which specifically hybridize with nucleic acids, preferably mRNA, encoding **FAK**.

SUMM [0015] This relationship between an **antisense** compound such as an oligonucleotide and its complementary nucleic acid target, to which it hybridizes, is commonly referred to as "**antisense**". "Targeting" an oligonucleotide to a chosen nucleic acid target, in the context of this invention, is a multistep process. The. . . state, or a foreign nucleic acid from an infectious agent. In the present invention, the targets are nucleic acids encoding **FAK**; in other words, a gene encoding **FAK**, or mRNA expressed from the **FAK** gene. mRNA which encodes **FAK** is presently the preferred target. The targeting process also includes determination of a site or sites within the nucleic acid sequence for the **antisense** interaction to occur such that modulation of gene expression will result.

SUMM . . . codon or codons that are used in vivo to initiate translation of an mRNA molecule transcribed from a gene encoding **FAK**, regardless of the sequence(s) of such codons. It is also known in the art that a translation termination codon (or. . .

SUMM . . . also be preferred. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM [0022] Hybridization of **antisense** oligonucleotides with mRNA interferes with one or more of the normal functions of MRNA. The functions of mRNA to be. . . may be engaged in by the RNA. Binding of specific protein(s) to the RNA may also be interfered with by **antisense** oligonucleotide hybridization to the RNA.

SUMM [0023] The overall effect of interference with MRNA function is modulation of expression of **FAK**. In the context of this invention "modulation" means either inhibition or stimulation; i.e., either a decrease or increase in expression.. . .

SUMM . . . therapeutics, prophylaxis, and as research reagents and in kits. Since the oligonucleotides of this invention hybridize to nucleic acids encoding **FAK**, sandwich, calorimetric and other assays can easily be constructed to exploit this fact. Provision of means for detecting hybridization of oligonucleotide with the **FAK** genes

or mRNA can routinely be accomplished. Such provision may include enzyme conjugation, radiolabelling or any other suitable detection systems. Kits for detecting the presence or absence of **FAK** may also be prepared.

SUMM [0028] The **antisense** compounds in accordance with this invention preferably comprise from about 5 to about 50 nucleobases. Particularly preferred are **antisense** oligonucleotides comprising from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides). As is. . .

SUMM [0029] Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al. (Angewandte Chemie, International Edition 1991, 30, 613-722), and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications 1993, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications 1993, CRC Press, Boca Raton, pages 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of **antisense** inhibition of gene expression. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated. . . hybridization techniques known in the art.

This RNAse H-mediated cleavage of the RNA target is distinct from the use of **ribozymes** to cleave nucleic acids. **Ribozymes** are not comprehended by the present invention.

SUMM . . . oligonucleotide, and may be chimeric oligonucleotides. Aside from or in addition to 2'-O-methoxyethyl modifications, oligonucleotides containing other modifications which enhance **antisense** efficacy, potency or target affinity are also preferred. Chimeric oligonucleotides comprising one or more such modifications are presently preferred.

SUMM [0045] The **antisense** compounds of the present invention include bioequivalent compounds, including pharmaceutically acceptable salts and prodrugs. This is intended to encompass any. . .

SUMM . . . procarbazine, hexamethylmelamine, pentamethylmelamine, mitoxantrone, amsacrine, chlorambucil, methylcyclohexylnitrosurea, nitrogen mustards, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-azacytidine, hydroxyurea, deoxycoformycin, 4-hydroxyperoxycyclophosphoramide, 5-fluorouracil (**5-FU**), 5-fluorodeoxyuridine (5-FUdR), methotrexate (MTX), colchicine, taxol, vincristine, vinblastine, etoposide, trimetrexate, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, The Merck Manual. . . al., eds., Rahway, N.J. When used with the compounds of the invention, such chemotherapeutic agents may be used individually (e.g., **5-FU** and oligonucleotide), sequentially (e.g., **5-FU** and oligonucleotide for a period of time followed by MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., **5-FU**, MTX and oligonucleotide, or **5-FU**, radiotherapy and oligonucleotide).

DETD [0111] Human **FAK** Oligonucleotide Sequences **Antisense** oligonucleotides were designed to target human **FAK**. Target sequence data are from the **focal adhesion kinase** (**FAK**) cDNA sequence published by Whitney, G.

S., et al. (DNA Cell Biol., 1993, 12, 823-830); Genbank accession number
L13616, provided. . .
DETD . . . Ill.), a positively charged nylon membrane. Immobilized RNA was
cross-linked by exposure to UV light. Membranes were probed with either **FAK** or glyceraldehyde 3-phosphate dehydrogenase (G3PDH) probes.
The probes were labeled by random primer using the PRIME-A-GENE.sup.7 Labeling System, Promega, Madison,. . .
DETD [0115] Results of an initial screen of the **FAK** **antisense** oligonucleotides are shown in Tables 5 (20 mers) and 6 (15 ers). Oligonucleotides 15392 (SEQ ID NO. 3), 15394 (SEQ. . . 30),
15408 (SEQ ID NO. 31) and 15412 (SEQ ID NO. 33) resulted in about 50% or
greater inhibition of **FAK** mRNA expression in this assay.
Oligonucleotides 15401 (SEQ ID NO. 8), 15403 (SEQ ID NO. 9), 15409 (SEQ ID NO.. . . 14), 15415 (SEQ ID NO. 15), and 15421 (SEQ ID NO. 18) resulted in about 80% or greater inhibition of **FAK** mRNA expression.
TABLE 1

Nucleotide Sequences of Human **FAK** Chimeric (deoxy gapped)
20 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE.sup.1 (5' .fwdarw. 3')	SEQ ID NO:	TARGET GENE NUCLEOTIDE CO-ORDINATES.sup.2. . .	GENE TARGET

DETD [0116]
TABLE 2

Nucleotide Sequences of Human **FAK**
20 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE.sup.1 (5' .fwdarw. 3')	SEQ ID NO:	TARGET GENE NUCLEOTIDE CO-ORDINATES.sup.2	GENE TARGET REGION
15432	CCGCGGGCTCACA	3. . .		

DETD [0117]
TABLE 3

Nucleotide Sequences of Human **FAK** Chimeric (deoxy gapped)
15 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE.sup.1 (5' .fwdarw. 3')	SEQ ID NO:	TARGET GENE NUCLEOTIDE CO-ORDINATES.sup.2. . .	GENE TARGET

DETD [0118]
TABLE 4

Nucleotide Sequences of Human **FAK**
15 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE.sup.1 (5' .fwdarw. 3')	SEQ ID NO:	TARGET GENE NUCLEOTIDE CO-ORDINATES.sup.2	GENE TARGET REGION
15433	GCGGGCTCACAGT	23. . .		

DETD [0119]
TABLE 5

Inhibition of Human **Fak** mRNA expression in A549 Cells by **FAK** 20 mer **Antisense** Oligonucleotides

SEQ	GENE

ISIS No:	SEQ ID NO:	TARGET REGION	% mRNA EXPRESSION	% mRNA INHIBITION
control	--	--	100%	0%
15392	3	5'-UTR. . .		

DETD [0120]
TABLE 6

Inhibition of Human **Fak** mRNA expression in A549 Cells by **FAK** 15 mer **antisense** oligonucleotides

ISIS No:	SEQ ID NO:	GENE TARGET REGION	% mRNA EXPRESSION	% mRNA INHIBITION
control	--	--	100%	0%
15393	23	5'-UTR. . .		

DETD [0121] Dose Response of **Antisense** Phosphorothioate Oligonucleotide Effects on **FAK** Levels in A549 Cells

DETD . . . showed IC.sub.50s of 50 nM or less and maximal inhibition seen was 95%.

TABLE 7

Dose Response of A549 cells to **FAK** Phosphorothioate Oligonucleotides

ISIS #	SEQ ID NO:	ASO Gene Target	Dose	% mRNA Expression	% mRNA Inhibition
control	--	--	--	100.0%	--
15932. . .					

DETD . . . as shown in Table 3. The LIPOFECTIN.sup.R to oligonucleotide ratio was maintained at 3 mg/ml LIPOFECTIN.sup.R per 100 nM oligonucleotide. **FAK** protein levels were determined 48 hours after **antisense** treatment in whole cell lysates by anti-**FAK** blotting. Cells on 10cm plates were lysed with 0.5 ml modified RIPA lysis buffer, diluted with 0.5 ml HNTG buffer. . . 150 mM NaCl, 0.1% Triton X-100, 10% glycerol), incubated with agarose beads, and cleared by centrifugation. Immunoprecipitations with a polyclonal **FAK** antibody (Salk Institute of Biological Studies, La Jolla, Calif.; additional **FAK** antibodies available from Upstate Biotechnology Incorporated, Lake Placid, N.Y.) were performed for 4 hr at 4.degree. C., collected on protein. . .

DETD [0125] Results are shown in Table 8.

TABLE 8

Dose Response of A549 cells to **FAK** Phosphorothioate Oligonucleotides

ISIS #	SEQ ID NO:	ASO Gene Target	Dose	% protein Expression	% protein Inhibition
control	--	--	--	100%	--
15409. . .					

DETD [0126] Effect of **FAK Antisense** Phosphorothioate Oligonucleotides on Growth Factor Stimulated Migration and Invasion

DETD [0127] Integrin-regulated **focal adhesion kinase** (**FAK**) is an important component of epidermal (EGF) and platelet-drived (PDGF) growth factor-induced motility of primary fibroblasts, smooth muscle, and adenocarcinoma cells. To measure the effect of **FAK antisense** oligonucleotides on cell migration, a modified Boyden chamber (Millipore, Bedford, Mass.) assay

was used (Sieg, D. J., et al., J.. . .
DETD . . . ID NO. 43) is a five base mismatch control oligonucleotide for ISIS 15421 (SEQ ID NO. 18).
TABLE 9

Effect of **FAK Antisense** Phosphorothioate Oligonucleotides on EGF-Stimulated Cell Migration

ISIS #	SEQ ID NO:	ASO Gene Target	EGF (ng/ml)	A.sub.600
control	--	--. . .		

DETD [0129] **FAK antisense** oligonucleotides were tested in an in vitro invasion assay using an .about.1 mm MATRIGEL.sup.R (Becton Dickinson, Franklin Lakes, N.J.) basement. . .
DETD [0130] Results are shown in Table 10.
TABLE 10

Effect of **FAK Antisense** Phosphorothioate Oligonucleotides on Tumor Cell Invasion

ISIS #	SEQ ID NO:	ASO Gene Target	MATRIGEL.sup.R (.mu.g/chamber)	Migration (A.sub.600)
control	--	--	0	8.3
15421	18. . .			

DETD [0131] **FAK Antisense** Oligonucleotides in a Retinal Neovascularization Model
DETD [0132] **FAK antisense** oligonucleotides were tested in a rabbit model of retinal neovascularization (Kimura, H., et al., Invest. Opthalmol. Vis. Sci., 1995, 36,. . .
DETD . . . be detected in the first week and retinal hemorrhaging began by the end of the third week. Animals receiving the **antisense** **FAK** oligonucleotide showed no evidence of retinal neovascularization over a four week period.
DETD [0134] Effect of **FAK Antisense** Phosphorothioate Pligonucleotide (ISIS 15421) Alone and in Combination with 5-Flurouracil on the Viability of Melanoma Cell Lines
DETD [0135] Inhibition of **FAK** in tumor cell lines causes cell rounding, loss of adhesion, and apoptosis which suggests a role for these inhibitors in the treatment of metastatic conditions. In these studies, an **antisense** inhibitor of **FAK** was tested alone and in combination with the chemotherapeutic agent, **5-FU** for its effects on melanoma cell line viability. C8161 and BL human melanoma cell lines were treated with ISIS 15421. . . 44) using the lipofectin protocol described herein. Oligonucleotides were transfected for four hours at 300 nM in lipofectin reagent and **5-FU** (200 .mu.g/mL; SIGMA) was added after the incubation for 20 hours. Cell viability was determined by the MTT assay. Loss of adhesion and apoptosis were determined by cell counting and the TUNEL assay, respectively. **FAK** expression was assayed by Western blot, probing with the anti-**FAK** clone 4.47 antibody (Upstate Biotechnology, Lake Placid, N.Y.).
DETD . . . cell line, treatment with ISIS 15421 resulted in a 23% reduction in cell viability compared to control ($p<0.0001$). Addition of **5-FU** to the **antisense** treated cells resulted in a significant further reduction in cell viability (69%; $p<0.0001$) compared to treatment with ISIS 15421 or **5-FU** alone (4.4% reduction; $p=0.15$) or the control oligonucleotide, ISIS 29848. Similar results were seen with the C8161 cell line.
DETD . . . cell adhesion and an increase in apoptosis. Western blots showed that treatment with ISIS 15421 resulted in a decrease of **FAK** protein expression. **FAK** protein levels were

decreased in BL melanoma cells upon treatment with **5-FU** alone and were undetectable upon treatment with the combination of ISIS 15421 and **5-FU**. These studies suggest that ISIS 15421, in combination with the chemotherapeutic agent **5-FU**, may be a useful in the treatment of melanoma.

DETD [0138] Effect of **FAK Antisense** Phosphorothioate Oligonucleotide (ISIS 15421) on Human Melanoma Xenograft Tumor Growth in Mice

DETD [0139] Another model used to investigate the efficacy of **antisense** oligonucleotides on tumor growth involves the use of mice transplanted with human cancer cells or cell line tumors. In these.

. .

DETD [0140] At the end of the timecourse, mice were sacrificed and tumor volumes measured. Tumor volumes in the **antisense** treated mice were significantly smaller than tumor volumes in control-treated mice with no observation of toxicity to the mice. Additionally, one third of the control-treated mice had grossly evident intraperitoneal metastases, while none of the **antisense**-treated mice displayed such metastases. These studies suggest that **antisense** oligonucleotides represent potential chemotherapeutic agents in the treatment of melanoma and the prevention of tumor metastasis.

CLM What is claimed is:

1. An **antisense** compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, translational termination region or 3' untranslated region of a nucleic acid molecule encoding **focal adhesion kinase**, wherein said **antisense** compound inhibits the expression of said **focal adhesion kinase**.

2. The **antisense** compound of claim 1 which is an **antisense** oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide has a sequence comprising SEQ ID NO: 3, 4, 6, 7, 8, 9, 16, 17, 18, 20 or 23.

. . .

4. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

5. The **antisense** compound of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage.

6. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

7. The **antisense** compound of claim 6 wherein the modified sugar moiety is a 2'-O-methoxyethyl moiety.

8. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

9. The **antisense** compound of claim 8 wherein the modified nucleobase is a 5-methyl cytosine.

10. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

11. A pharmaceutical composition comprising the **antisense** compound of claim 1 and a pharmaceutically acceptable carrier or

diluent.

13. The pharmaceutical composition of claim 11 wherein the **antisense** compound is an **antisense** oligonucleotide.

17. A method of inhibiting the expression of **focal adhesion kinase** in cells or tissues comprising contacting said cells or tissue with the **antisense** compound of claim 1 so that expression of **focal adhesion kinase** is inhibited.

18. An **antisense** compound up to 30 nucleobases in length targeted to the coding region, or start site of a nucleic acid molecule encoding **focal adhesion kinase**, wherein said **antisense** compound inhibits the expression of said **focal adhesion kinase** and has a sequence comprising at least an 8 nucleobasic portion of SEQ ID NO: 10, 11, 12, 14, 15,. . .

19. The **antisense** compound of claim 18 which is an **antisense** oligonucleotide.

20. The **antisense** compound of claim 19 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

21. The **antisense** compound of claim 20 wherein the modified internucleoside linkage is a phosphorothioate linkage.

22. The **antisense** compound of claim 19 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

23. The **antisense** compound of claim 22 wherein the modified sugar moiety is a 2'-O-methoxyethyl moiety.

24. The **antisense** compound of claim 19 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

25. The **antisense** compound of claim 24 wherein the modified nucleobase is a 5-methyl cytosine.

26. The **antisense** compound of claim 19 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

27. A pharmaceutical composition comprising the **antisense** compound of claim 18 and a pharmaceutically acceptable carrier or diluent.

29. The pharmaceutical composition of claim 27 wherein the **antisense** compound is an **antisense** oligonucleotide.

33. A method of inhibiting the expression of **focal adhesion kinase** in cells or tissues comprising contacting said cells or tissue with the **antisense** compound of claim 18 so that expression of **focal adhesion kinase** is inhibited.

34. A method of treating an animal having a disease or condition associated with **focal adhesion kinase** comprising administering to said animal a therapeutically or prophylactically effective amount of an **antisense** compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human **focal adhesion kinase** wherein said **antisense** compound inhibits the expression of human

focal adhesion kinase.

39. A method of preventing migration of cells associated with expression of **focal adhesion kinase** comprising administering to said cells a therapeutically or prophylactically effective amount of an **antisense** compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human **focal adhesion kinase** wherein said **antisense** compound inhibits the expression of human **focal adhesion kinase.**

40. A method of preventing neovascularization associated with expression of **focal adhesion kinase** in an animal comprising administering to said animal a therapeutically or prophylactically effective amount of an **antisense** compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human **focal adhesion kinase** wherein said **antisense** compound inhibits the expression of human **focal adhesion kinase.**

41. A method of treating an animal having a disease or condition associated with **focal adhesion kinase** comprising administering to said animal a therapeutically or prophylactically effective amount of an **antisense** compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human **focal adhesion kinase** in combination with a therapeutically or prophylactically effective amount of a chemotherapeutic agent.

L4 ANSWER 2 OF 37 USPATFULL

ACCESSION NUMBER:	2001:221154 USPATFULL			
TITLE:	SH2 domain-containing peptides			
INVENTOR(S):	Stewart, Timothy A., San Francisco, CA, United States Lu, Yanmei, Belmont, CA, United States			
PATENT ASSIGNEE(S):	Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6326482	B1	20011204	
	WO 9954467		19991028	
APPLICATION INFO.:	US 1999-367206		19990809	(9)
	WO 1999-US8847		19990423	
			19990809	PCT 371 date
			19990809	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	US 1998-82767		19980423	(60)
	US 1998-11329		19981222	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Schwartzman, Robert A.			
ASSISTANT EXAMINER:	Davis, Katharine F			
LEGAL REPRESENTATIVE:	Barnes, Elizabeth M.			
NUMBER OF CLAIMS:	21			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	39 Drawing Figure(s); 29 Drawing Page(s)			
LINE COUNT:	4794			

SUMM . . . blocks, inhibits and/or neutralizes the normal functioning of

the latter compounds in cellular signaling, including both small bioorganic molecules and **antisense** nucleotides.

SUMM . . . 1312 or about 1555 to about 2150 of FIG. 3 (SEQ ID NO:6). Such nucleic acid molecules can act as **antisense** molecules of the amplified genes identified herein, which, in turn, can find use in the modulation of the respective amplified genes, or as **antisense** primers in amplification reactions. Furthermore, such sequences can be used as part of **ribozyme** and/or triple helix sequence which, in turn, may be used in regulation of the amplified genes.

SUMM . . . PRO309 polypeptide. The agent preferably is an anti-PRO201, anti-PRO308 or anti-PRO309 antibody, a small organic and inorganic molecule, peptide, phosphopeptide, **antisense** or **ribozyme** molecule, or a triple helix molecule. In a specific aspect, the agent, e.g. anti-PRO201, anti-PRO308 or anti-PRO309 antibody induces cell. . .

DETD . . . peptidomimetics, pharmacological agents and their metabolites, transcriptional and translation control sequences, and the like. Another preferred form of antagonist includes **antisense** nucleotides that inhibit the PRO201, PRO308 or PRO309 modulated signaling. Preferred forms bind to specific regions on either PRO201, PRO308. . .

DETD . . . etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), **5-FU**, 6-thioguanine, 6-mercaptopurine, actinomycin D, VP-16, chlorambucil, melphalan, and other related nitrogen mustards. Also included in this definition are hormonal agents.

. .

DETD . . . outcome in response to these extracellular signals could be quite distinct in the presence or absence of Nsp1. For example, **FAK** associates with the SH3 region of Cas via a PXXP region at the C-terminus of **FAK** P(715)SRP--mouse nomenclature (Harte et al., J. Biol. Chem. 271: 13649-55 (1996). There are six PXXP signatures in Nsp1 (SEQ ID. . . NO:1). This raises the possibility that Nsp1 could compete for the SH3 region on Cas and decrease the amount of **Fak** that is bound to Cas and so alter **Fak** dependent events. The data also point to an EGF mediated decrease in the extent of phosphorylation of the Cas that. . .

DETD . . . associated with the amplification of the genes identified herein include, without limitation, antibodies, small organic and inorganic molecules, peptides, phosphopeptides, **antisense** and **ribozyme** molecules, triple helix molecules, etc. that inhibit the expression and/or activity of the target gene product.

DETD For example, **antisense** RNA and RNA molecule act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. When **antisense** DNA is used, oligodeoxyribonucleotides derived from the translation initiation site, e.g. between about -10 and +10 position of the target. . .

DETD **Ribozymes** are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. **Ribozymes** act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific **ribozyme** cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g. Rossi, Current. . .

DETD (2) **Antisense** Nucleolides

DETD Another preferred class of antagonists involves the use of gene therapy techniques, include the administration of **antisense** nucleotides. Applicable gene therapy techniques include single or multiple administrations of therapeutically effective DNA or mRNA. **Antisense** RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes in vivo. Short **antisense** oligonucleotides can be imported into cells where they

act as inhibitors, despite their low intracellular concentrations caused
by restricted uptake. . .
DETD . . . PRO309 expression may be reduced by providing PRO201-, PRO308- or PRO309-expressing cells with an amount of PRO201, PRO308 or PRO309 **antisense** RNA or DNA effective to reduce expression of the PRO201, PRO308 or PRO309 protein.
DETD . . . of PRO201, PRO308 or PRO309 may be reduced by providing PRO201,
PRO308 or PRO309 expressing cells with an amount of **antisense** RNA or DNA effective for reduced expression of the binding partners of PRO201, PRO308 or PRO309.
DETD . . . to be treated with such antibodies and other compounds, including, but not limited to, small organic and inorganic molecules, peptides, **antisense** molecules, etc. include benign or malignant tumors (e.g. renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, ling, vulval,. . .
DETD . . . Rozengurt, J. Biol. Chem. 272; 9363-70 (1997); Nojima et al., J. Biol. Chem. 270: 15398-402 (1995). Cas directly interacts with **focal adhesion kinase** (**FAK**)[Polte & Hanks, Proc. Natl. Acad. Sci. USA 92: 10678-82 (1995)] and appears to be a critical component by which extracellular. . .
DETD . . . at 37.degree. C., and further processed for in situ hybridization as described by Lu and Gillett, supra. A[.sup.33 -P] UTP-labeled **antisense** niboprobe was generated from a PCR product and hybridized at 55.degree. C. overnight. The slides were dipped in Kodak NTB2. . .
DETD Comparable background signal observed with sense and **antisense** probes in many tissues. The only sites where expression appeared to be specific were fetal thymic medulla, fetal spleen, epithelium. . .
DETD Examination of cell pellets showed the SHC transfected cells were positive with both sense and **antisense** probes making interpretation of this study problematic. The SW480 cells were negative with both probes. For the colon cancers only. . .

L4 ANSWER 3 OF 37 USPATFULL
ACCESSION NUMBER: 2001:36655 USPATFULL
TITLE: **Antisense** inhibition of SHP-2 expression
INVENTOR(S): Bennett, C. Frank, Carlsbad, CA, United States
Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6200807	B1	20010313	
APPLICATION INFO.:	US 1999-358683		19990721	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 2592
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Antisense** inhibition of SHP-2 expression
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of SHP-2. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding SHP-2. Methods of using these compounds for modulation of SHP-2 expression and for treatment. . .
SUMM The present invention provides compositions and methods for modulating the expression of SHP-2. In particular, this invention relates to **antisense** compounds, particularly oligonucleotides, specifically

hybridizable with nucleic acids encoding human SHP-2. Such oligonucleotides have been shown to modulate the expression. . .

SUMM In concert with **focal adhesion kinase**, SHP-2 has been shown to regulate chemotaxis in human breast adenocarcinoma cells. In these cells, it was demonstrated that, upon growth factor stimulation, **focal adhesion kinase** was dephosphorylated by SHP-2 which in turn increased cell adhesion. Alternatively, expression of a dominant negative mutant of SHP-2, lacking. . .

SUMM . . . been shown that SHP-2 plays a critical role in the allergic response system. Interleukin 5 promotes eosinophil survival and an **antisense** oligonucleotide targeting SHP-2 was shown to inhibit this response indicating that SHP-2 plays a positive role in the activation of. . .

SUMM **Antisense** technology is emerging as an effective means for reducing the expression of specific gene products and may therefore prove to. . .

SUMM The present invention is directed to **antisense** compounds, particularly oligonucleotides, which are targeted to a nucleic acid encoding SHP-2, and which modulate the expression of SHP-2. Pharmaceutical and other compositions comprising the **antisense** compounds of the invention are also provided. Further provided are methods of modulating the expression of SHP-2 in cells or tissues comprising contacting said cells or tissues with one or more of the **antisense** compounds or compositions of the invention. Further provided are methods of treating an animal, particularly a human, suspected of having. . . condition associated with expression of SHP-2 by administering a therapeutically or prophylactically effective amount of one or more of the **antisense** compounds or compositions of the invention.

SUMM The present invention employs oligomeric **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding SHP-2, ultimately modulating the amount of SHP-2 produced. This is accomplished by providing **antisense** compounds which specifically hybridize with one or more nucleic acids encoding SHP-2. As used herein, the terms "target nucleic acid". . . modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "**antisense**". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with. . .

SUMM It is preferred to target specific nucleic acids for **antisense**. "Targeting" an **antisense** compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins. . . acid molecule encoding SHP-2. The targeting process also includes determination of a site or sites within this gene for the **antisense** interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within. . .

SUMM . . . also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM . . . between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an **antisense** compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An **antisense** compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal. . . to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the **antisense** compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of. . .

SUMM **Antisense** compounds are commonly used as research reagents and diagnostics. For example, **antisense** oligonucleotides, which

are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. **Antisense** compounds are also used, for example, to distinguish between functions of various members of a biological pathway. **Antisense** modulation has, therefore, been harnessed for research use.

SUMM The specificity and sensitivity of **antisense** is also harnessed by those of skill in the art for therapeutic uses. **Antisense** oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. **Antisense** oligonucleotides have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established. . .

SUMM While **antisense** oligonucleotides are a preferred form of **antisense** compound, the present invention comprehends other oligomeric **antisense** compounds, including but not limited to oligonucleotide mimetics such as are described below. The **antisense** compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides). Particularly preferred **antisense** compounds are **antisense** oligonucleotides, even more preferably those comprising from about 12 to about 25 nucleobases. As is known in the art, a. . .

SUMM Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press, 1993. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes **antisense** compounds which are chimeric compounds. "Chimeric" **antisense** compounds or "chimeras," in the context of this invention, are **antisense** compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit,. . .

SUMM Chimeric **antisense** compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide. . .

SUMM The **antisense** compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase. . .

SUMM The **antisense** compounds of the invention are synthesized in vitro and do not include **antisense** compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of **antisense** molecules. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures. . .

SUMM The **antisense** compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which,. . .

SUMM The **antisense** compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. For therapeutics,. . . of having a disease or disorder which can be treated by modulating the expression of SHP-2 is treated by administering **antisense** compounds in accordance

with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an **antisense** compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the **antisense** compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation or tumor. . .

SUMM The **antisense** compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding SHP-2, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the **antisense** oligonucleotides of the invention with a nucleic acid encoding SHP-2 can be detected by means known in the art. Such. . .

SUMM The present invention also includes pharmaceutical compositions and formulations which include the **antisense** compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending. . .

SUMM . . . No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include an **antisense** RNA. U.S. Pat. No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in liposomes. WO 97/04787 to Love et al. discloses liposomes comprising **antisense** oligonucleotides targeted to the raf gene.

SUMM . . . can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., **Antisense** Res. Dev., 1995, 5, 115-121; Takakura et al., **Antisense** & Nucl. Acid Drug Dev., 1996, 6, 177-183).

SUMM Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more **antisense** compounds and (b) one or more other chemotherapeutic agents which function by a non-**antisense** mechanism. Examples of such chemotherapeutic agents include, but are not limited to, anticancer drugs such as daunorubicin, dactinomycin, doxorubicin, bleomycin, mitomycin, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-fluorouracil (**5-FU**), floxuridine (5-FUdR), methotrexate (MTX), colchicine, vincristine, vinblastine, etoposide, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, The Merck Manual of Diagnosis. . . Manual of Diagnosis and Therapy, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). Other non-**antisense** chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used together or. . .

SUMM In another related embodiment, compositions of the invention may contain one or more **antisense** compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional **antisense** compounds targeted to a second nucleic acid target. Numerous examples of **antisense** compounds are known in the art. Two or more combined compounds may be used together or sequentially.

DETD The effect of **antisense** compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the. . .

DETD Treatment with **antisense** compounds:

DETD **Antisense** modulation of SHP-2 expression can be assayed in a variety of ways known in the art. For example, SHP-2 mRNA. . .

DETD . . . dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after **antisense** oligonucleotide treatment of test samples.

DETD Eighteen hours after **antisense** treatment, cell monolayers were

washed twice with cold PBS and lysed in 1 mL RNAZOL.TM. (TEL-TEST "B" Inc., Friendswood, Tex.).. . .

DETD **Antisense** Inhibition of SHP-2 Expression--Phosphorothioate Oligodeoxynucleotides

DETD **Antisense** Inhibition of SHP-2 Expression--Phosphorothioate 2'-MOE Gapmer Oligonucleotides

CLM What is claimed is:

1. An **antisense** compound 8 to 30 nucleobases in length targeted to a 5' untranslated region, a start codon, nucleotides 298 through 1883. . . of a coding region, a stop codon, or a 3' untranslated region of human SHP-2 (SEQ ID NO:1), wherein said **antisense** compound specifically hybridizes with and inhibits the expression of human SHP-2.

2. The **antisense** compound of claim 1 which is an **antisense** oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

4. The **antisense** compound of claim 3 wherein the modified internucleoside linkage is a phosphorothioate linkage.

5. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

6. The **antisense** compound of claim 5 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

7. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

8. The **antisense** compound of claim 7 wherein the modified nucleobase is a 5-methylcytosine.

9. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

10. An **antisense** compound up to 30 nucleobases in length comprising at least an 8-nucleobase portion of SEQ ID NO: 10, 9, 11,.

.

11. The **antisense** compound of claim 10 which is an **antisense** oligonucleotide.

12. The **antisense** compound of claim 11 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

13. The **antisense** compound of claim 12 wherein the modified internucleoside linkage is a phosphorothioate linkage.

14. The **antisense** compound of claim 11 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

15. The **antisense** compound of claim 14 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

16. The **antisense** compound of claim 11 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

17. The **antisense** compound of claim 16 wherein the modified nucleobase is a 5-methylcytosine.

18. The **antisense** compound of claim 11 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

. . . inhibiting the expression of human SHP-2 in cells or tissues comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 1 so that expression of human SHP-2 is inhibited.

. . . the expression of human SHP-2 in human cells or tissues comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 3 so that expression of human SHP-2 is inhibited.

L4 ANSWER 4 OF 37 USPATFULL

ACCESSION NUMBER:	2001:10735 USPATFULL
TITLE:	**Antisense** modulation of integrin-linked kinase expression
INVENTOR(S):	Bennett, C. Frank, Carlsbad, CA, United States Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S):	ISIS Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6177273	B1	20010123	
APPLICATION INFO.:	US 1999-428219		19991026	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Guzo, David
ASSISTANT EXAMINER:	McGarry, Sean
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
LINE COUNT:	2549

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Antisense** modulation of integrin-linked kinase expression

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of Integrin-linked kinase. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding Integrin-linked kinase. Methods of using these compounds for modulation of Integrin-linked kinase expression and. . .

SUMM The present invention provides compositions and methods for modulating the expression of Integrin-linked kinase. In particular, this invention relates to **antisense** compounds, particularly oligonucleotides, specifically hybridizable with nucleic acids encoding human Integrin-linked kinase. Such oligonucleotides have been shown to modulate the. . .

SUMM . . . been shown to interact with actin filaments of the cytoskeleton and with cytoplasmic proteins such as talin, paxillin, filamin and **focal adhesion kinase** (**FAK**) (LaFlamme et al., Matrix Biol., 1997, 16, 153-163). Recently, four additional proteins that interact with .beta.-integrin subunit cytoplasmic domains were. . .

SUMM **Antisense** technology is emerging as an effective means for reducing the expression of specific gene products and may therefore prove to. . . for the modulation of integrin-linked kinase expression. The present invention provides compositions and methods for modulating integrin-linked kinase expression using **antisense** technology.

SUMM The present invention is directed to **antisense** compounds, particularly oligonucleotides, which are targeted to a nucleic acid

encoding Integrin-linked kinase, and which modulate the expression of Integrin-linked kinase. Pharmaceutical and other compositions comprising the **antisense** compounds of the invention are also provided. Further provided are methods of modulating the expression of Integrin-linked kinase in cells or tissues comprising contacting said cells or tissues with one or more of the **antisense** compounds or compositions of the invention. Further provided are methods of treating an animal, particularly a human, suspected of having. . . associated with expression of Integrin-linked kinase by administering a therapeutically or prophylactically effective amount of one or more of the **antisense** compounds or compositions of the invention.

SUMM The present invention employs oligomeric **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding Integrin-linked kinase, ultimately modulating the amount of Integrin-linked kinase produced. This is accomplished by providing **antisense** compounds which specifically hybridize with one or more nucleic acids encoding Integrin-linked kinase. As used herein, the terms "target nucleic. . . modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "**antisense**". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with. . .

SUMM It is preferred to target specific nucleic acids for **antisense**. "Targeting" an **antisense** compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins. . . molecule encoding Integrin-linked kinase. The targeting process also includes determination of a site or sites within this gene for the **antisense** interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within. . .

SUMM . . . also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM . . . between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an **antisense** compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An **antisense** compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal. . . to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the **antisense** compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of. . .

SUMM **Antisense** compounds are commonly used as research reagents and diagnostics. For example, **antisense** oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. **Antisense** compounds are also used, for example, to distinguish between functions of various members of a biological pathway. **Antisense** modulation has, therefore, been harnessed for research use.

SUMM The specificity and sensitivity of **antisense** is also harnessed by those of skill in the art for therapeutic uses. **Antisense** oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. **Antisense** oligonucleotides have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established. . .

SUMM While **antisense** oligonucleotides are a preferred form of

antisense compound, the present invention comprehends other oligomeric **antisense** compounds, including but not limited to oligonucleotide mimetics such as are described below. The **antisense** compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides). Particularly preferred **antisense** compounds are **antisense** oligonucleotides, even more preferably those comprising from about 12 to about 25 nucleobases. As is known in the art, a. . .

SUMM Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press, 1993. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes **antisense** compounds which are chimeric compounds. "Chimeric" **antisense** compounds or "chimeras," in the context of this invention, are **antisense** compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit,. . .

SUMM Chimeric **antisense** compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide. . .

SUMM The **antisense** compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase. . .

SUMM The **antisense** compounds of the invention are synthesized in vitro and do not include **antisense** compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of **antisense** molecules. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures. . .

SUMM The **antisense** compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which,. . .

SUMM The **antisense** compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. For therapeutics,. . . having a disease or disorder which can be treated by modulating the expression of Integrin-linked kinase is treated by administering **antisense** compounds in accordance with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an **antisense** compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the **antisense** compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation or tumor. . .

SUMM The **antisense** compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding Integrin-linked kinase, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the **antisense** oligonucleotides of the invention with a nucleic acid encoding Integrin-linked kinase can be detected by means known in the art.. . .

SUMM The present invention also includes pharmaceutical compositions and

formulations which include the **antisense** compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending. . .

SUMM . . . No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include an **antisense** RNA. U.S. Pat. No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in liposomes. WO 97/04787 to Love et al. discloses liposomes comprising **antisense** oligonucleotides targeted to the raf gene.

SUMM . . . can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., **Antisense** Res. Dev., 1995, 5, 115-121; Takakura et al., **Antisense** & Nucl. Acid Drug Dev., 1996, 6, 177-183).

SUMM Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more **antisense** compounds and (b) one or more other chemotherapeutic agents which function by a non-**antisense** mechanism. Examples of such chemotherapeutic agents include, but are not limited to, anticancer drugs such as daunorubicin, dactinomycin, doxorubicin, bleomycin, mitomycin, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-fluorouracil (**5-FU**), floxuridine (5-FUdR), methotrexate (MTX), colchicine, vincristine, vinblastine, etoposide, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, The Merck Manual of Diagnosis. . . Manual of Diagnosis and Therapy, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). Other non-**antisense** chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used together or. . .

SUMM In another related embodiment, compositions of the invention may contain one or more **antisense** compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional **antisense** compounds targeted to a second nucleic acid target. Numerous examples of **antisense** compounds are known in the art. Two or more combined compounds may be used together or sequentially.

DETD The effect of **antisense** compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the. . .

DETD Treatment with **Antisense** Compounds:

DETD **Antisense** modulation of Integrin-linked kinase expression can be assayed in a variety of ways known in the art. For example, Integrin-linked. . .

DETD . . . dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after **antisense** oligonucleotide treatment of test samples.

DETD Eighteen hours after **antisense** treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL.TM. (TEL-TEST "B" Inc., Friendswood, Tex.).. . .

DETD **Antisense** Inhibition of Integrin-Linked Kinase Expression-Phosphorothioate 2'-MOE Gapmer Oligonucleotides

CLM What is claimed is:

1. An **antisense** compound 8 to 30 nucleobases in length targeted to nucleobases 1-120 of the 5' UTR region nucleobases 171-1507 of the. . . region, or the stop codon of a nucleic acid molecule encoding human Integrin-linked kinase (SEQ ID NO: 3), wherein said **antisense** compound specifically hybridizes with and inhibits the expression of human Integrin-linked kinase.

2. The **antisense** compound of claim 1 which is an

antisense oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide has a sequence comprising SEQ ID NO: 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24,. . .

4. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

5. The **antisense** compound of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage.

6. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

7. The **antisense** compound of claim 6 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

8. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

9. The **antisense** compound of claim 8 wherein the modified nucleobase is a 5-methylcytosine.

10. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

11. A composition comprising the **antisense** compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

13. The composition of claim 11 wherein the **antisense** compound is an **antisense** oligonucleotide.

. . . of Integrin-linked kinase in human cells or tissues in vitro comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 1 so that expression of Integrin-linked kinase is inhibited.

L4 ANSWER 5 OF 37 USPATFULL

ACCESSION NUMBER:	2000:138121 USPATFULL		
TITLE:	**Antisense** inhibition of **focal adhesion kinase** expression		
INVENTOR(S):	Monia, Brett P., LaCosta, CA, United States Gaarde, William A., Carlsbad, CA, United States		
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6133031		20001017
APPLICATION INFO.:	US 1999-377310		19990819 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Elliott, George C.		
ASSISTANT EXAMINER:	Lacourciere, Karen A		
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata		
NUMBER OF CLAIMS:	29		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2280		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Antisense** inhibition of **focal adhesion kinase** expression

AB Compounds, compositions and methods are provided for inhibiting

FAK mediated signaling. The compositions comprise **antisense** compounds targeted to nucleic acids encoding **FAK**. Methods of using these **antisense** compounds for inhibition of **FAK** expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of **FAK** are provided.

SUMM This invention relates to compositions and methods for modulating expression of the human **focal adhesion kinase** (**FAK**) gene, which encodes a signaling protein involved in growth factor response and cell migration and is implicated in disease. This invention is also directed to methods for inhibiting **FAK**-mediated signal transduction; these methods can be used diagnostically or therapeutically. Furthermore, this invention is directed to treatment of conditions associated with expression of the human **FAK** gene.

SUMM . . . be induced by both integrin receptor-mediated signals (haptotaxis migration) and/or soluble growth factor-mediated signals (chemotaxis migration). Integrin receptor engagement activates **focal adhesion kinase** (**FAK**, also **pp125FAK**), a non-receptor protein-tyrosine kinase localized to cell substratum-extracellular matrix (ECM) contact sites that function as part of a cytoskeletal-associated network of signaling proteins (Schlaepfer, D. D., et al., Prog. Biophys. Mol. Biol., 1999, 71, 435-478). In adherent cells, **FAK** is often associated with integrins at focal adhesions (Schaller, M. D., et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 5192-5196). Numerous other signaling proteins, including other protein tyrosine kinases are associated with **FAK** at these regions. Phosphorylation of **FAK** results in activation of the mitogen-activated protein kinase pathway. In addition, **FAK** regulates activation of phosphatidylinositol 3'-kinase which may serve to prevent apoptosis. **FAK** has also been shown to be required for internalization of bacteria mediated by invasin (Alrutz, M. A. and Isberg, R.. . .

SUMM Overexpression of **FAK** is involved in cancer progression. High levels of **FAK** correlates with invasiveness and metastatic potential in colon tumors (Weiner, T. M., et al., Lancet, 1993, 342, 1024-1025), breast tumors. . .

SUMM **FAK**'s role in cell migration has led to the speculation that it may be relevant in other diseases such as embryonic. . .

SUMM There is a lack of specific inhibitors of **FAK**.

Antisense approaches have been a means by which the function of **FAK** has been investigated. Lou, J. et al. (J. Orthopaedic Res., 1997, 15, 911-918) used an adenoviral based vector to express **antisense FAK** RNA to show that **FAK** is involved in wound healing in tendons. Another **antisense** **FAK** expression vector containing 400 bp of complementary sequence was used to study the interaction of type I collagen and .alpha.2.beta.1. . .

SUMM **Antisense** oligonucleotides have been used in several studies. Tanaka, S. et al. (J. Cell. Biochem., 1995, 58, 424-435) disclose two **antisense** phosphorothioate oligonucleotides targeted to the start site of mouse **FAK**. Xu, L. -H., et al. (Cell Growth Diff., 1996, 7, 413-418) disclose two **antisense** phosphorothioate oligonucleotides targeted within the coding region of human **FAK**. They also show that **FAK antisense** treatment could induce apoptosis in tumor cells. Sonoda, Y., et al. (Biochem. Biophys. Res. Comm., 1997, 241, 769-774) also demonstrated a role for **FAK** in apoptosis using **antisense** phosphorothioate oligonucleotides targeted to the start site and within the coding region of human **FAK**. Shibata, K., et al. (Cancer Res., 1998, 58, 900-903) disclose **antisense** phosphorothioate oligonucleotides targeted to the start site and coding region of human **FAK**. Narase, K., et al. (Oncogene, 1998, 17, 455-463) disclose an **antisense** phosphorothioate oligonucleotide targeted to the

start site of human **FAK**.

SUMM There remains a long-felt need for improved compositions and methods for inhibiting **FAK** gene expression.

SUMM The present invention provides **antisense** compounds which are targeted to nucleic acids encoding **focal adhesion kinase** expression (**FAK**) and are capable of modulating **FAK** mediated signaling. The present invention also provides chimeric oligonucleotides targeted to nucleic acids encoding human **FAK**. The **antisense** compounds of the invention are believed to be useful both diagnostically and therapeutically, and are believed to be particularly useful. . .

SUMM The present invention also comprises methods of modulating **FAK** mediated signaling, in cells and tissues, using the **antisense** compounds of the invention. Methods of inhibiting **FAK** expression are provided; these methods are believed to be useful both therapeutically and diagnostically. These methods are also useful as tools, for example, for detecting and determining the role of **FAK** in various cell functions and physiological processes and conditions and for diagnosing conditions associated with expression of **FAK**.

SUMM . . . cancers, including those of the colon, breast and mouth. These methods are believed to be useful, for example, in diagnosing **FAK**-associated disease progression. These methods employ the **antisense** compounds of the invention. These methods are believed to be useful both therapeutically, including prophylactically, and as clinical research and. . .

SUMM **FAK** plays important roles in integrin-mediated signal transduction. Overexpression of **FAK** is associated with tumor progression and metastatic potential. As such, this protein represents an attractive target for treatment of such diseases. In particular, modulation of the expression of **FAK** may be useful for the treatment of diseases such as colon cancer, breast cancer and cancer of the mouth.

SUMM The present invention employs **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding **FAK**, ultimately modulating the amount of **FAK** produced. This is accomplished by providing oligonucleotides which specifically hybridize with nucleic acids, preferably mRNA, encoding **FAK**.

SUMM This relationship between an **antisense** compound such as an oligonucleotide and its complementary nucleic acid target, to which it hybridizes, is commonly referred to as "**antisense**". "Targeting" an oligonucleotide to a chosen nucleic acid target, in the context of this invention, is a multistep process. The. . . state, or a foreign nucleic acid from an infectious agent. In the present invention, the targets are nucleic acids encoding **FAK**; in other words, a gene encoding **FAK**, or mRNA expressed from the **FAK** gene. mRNA which encodes **FAK** is presently the preferred target. The targeting process also includes determination of a site or sites within the nucleic acid sequence for the **antisense** interaction to occur such that modulation of gene expression will result.

SUMM . . . codon or codons that are used in vivo to initiate translation of an mRNA molecule transcribed from a gene encoding **FAK**, regardless of the sequence(s) of such codons. It is also known in the art that a translation termination codon (or. . .

SUMM . . . also be preferred. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM Hybridization of **antisense** oligonucleotides with mRNA interferes with one or more of the normal functions of mRNA. The functions of mRNA to be. . . may be engaged in by the RNA. Binding of

specific protein(s) to the RNA may also be interfered with by **antisense** oligonucleotide hybridization to the RNA.

SUMM The overall effect of interference with mRNA function is modulation of expression of **FAK**. In the context of this invention "modulation" means either inhibition or stimulation; i.e., either a decrease or increase in expression.. . .

SUMM . . . therapeutics, prophylaxis, and as research reagents and in kits. Since the oligonucleotides of this invention hybridize to nucleic acids encoding **FAK**, sandwich, calorimetric and other assays can easily be constructed to exploit this fact. Provision of means for detecting hybridization of oligonucleotide with the **FAK** genes or mRNA can routinely be accomplished. Such provision may include enzyme conjugation, radiolabelling or any other suitable detection systems. Kits for detecting the presence or absence of **FAK** may also be prepared.

SUMM The **antisense** compounds in accordance with this invention preferably comprise from about 5 to about 50 nucleobases. Particularly preferred are **antisense** oligonucleotides comprising from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides). As is. . .

SUMM Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al. (Angewandte Chemie, International Edition 1991, 30, 613-722), and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications 1993, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications 1993, CRC Press, Boca Raton, pages 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of **antisense** inhibition of gene expression. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated. . . hybridization techniques known in the art.

This RNAse H-mediated cleavage of the RNA target is distinct from the use of **ribozymes** to cleave nucleic acids. **Ribozymes** are not comprehended by the present invention.

SUMM . . . oligonucleotide, and may be chimeric oligonucleotides. Aside from or in addition to 21-O-methoxyethyl modifications, oligonucleotides containing other modifications which enhance **antisense** efficacy, potency or target affinity are also preferred. Chimeric oligonucleotides comprising one or more such modifications are presently preferred.

SUMM The **antisense** compounds of the present invention include bioequivalent compounds, including pharmaceutically acceptable salts and prodrugs. This is intended to encompass any. . .

SUMM . . . procarbazine, hexamethylmelamine, pentamethylmelamine, mitoxantrone, amsacrine, chlorambucil, methylcyclohexylnitrosurea, nitrogen mustards, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-azacytidine, hydroxyurea, deoxycoformycin, 4-hydroxyperoxycyclophosphoramide, 5-fluorouracil (**5-FU**), 5-fluorodeoxyuridine (5-FUdR), methotrexate (MTX), colchicine, taxol, vincristine, vinblastine, etoposide, trimetrexate, teniposide, cisplatin and diethylstilbestrol (DES). See,

generally, The Merck Manual. . . al., eds., Rahway, N.J. When used with the compounds of the invention, such chemotherapeutic agents may be used individually (e.g., **5-FU** and oligonucleotide), sequentially (e.g., **5-FU** and oligonucleotide for a period of time followed by MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., **5-FU**, MTX and oligonucleotide, or **5-FU**, radiotherapy and oligonucleotide).

DETD Human **FAK** Oligonucleotide Sequences

DETD **Antisense** oligonucleotides were designed to target human **FAK**. Target sequence data are from the **focal adhesion kinase** (**FAK**) cDNA sequence published by Whitney, G. S., et al. (DNA Cell Biol., 1993, 12, 823-830); Genbank accession number L13616, provided. . .

DETD . . . Ill.), a positively charged nylon membrane. Immobilized RNA was cross-linked by exposure to UV light. Membranes were probed with either **FAK** or glyceraldehyde 3-phosphate dehydrogenase (G3PDH) probes. The probes were labeled by random primer using the PRIME-A-GENE.RTM. Labeling System, Promega, Madison,. . .

DETD Results of an initial screen of the **FAK antisense** oligonucleotides are shown in Tables 5 (20 mers) and 6 (15 mers). Oligonucleotides 15392 (SEQ ID NO. 3), 15394 (SEQ. . . 30), 15408 (SEQ ID NO. 31) and 15412 (SEQ ID NO. 33) resulted in about 50% or greater inhibition of **FAK** mRNA expression in this assay. Oligonucleotides 15401 (SEQ ID NO. 8), 15403 (SEQ ID NO. 9), 15409 (SEQ ID NO.. . . 14), 15415 (SEQ ID NO. 15), and 15421 (SEQ ID NO. 18) resulted in about 80% or greater inhibition of **FAK** mRNA expression.

DETD TABLE 1

Nucleotide Sequences of Human **FAK** Chimeric (deoxy gapped) 20 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE (5' ->)	SEQUENCE ID NO.	TARGET NUCLEOTIDE CO-ORDINATES	GENE

DETD TABLE 2

Nucleotide Sequences of Human **FAK** 20 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE (5' -> 3')	SEQUENCE ID NO:	TARGET NUCLEOTIDE CO-ORDINATES	GENE

DETD TABLE 3

Nucleotide Sequences of Human **FAK** Chimeric (deoxy gapped) 15 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE (5' ->)	SEQUENCE ID NO.	TARGET NUCLEOTIDE CO-ORDINATES	GENE

DETD TABLE 4

Nucleotide Sequences of Human **FAK** 15 mer Phosphorothioate Oligonucleotides

ISIS NO.	NUCLEOTIDE SEQUENCE (5' -> 3')	SEQUENCE ID NO:	TARGET NUCLEOTIDE CO-ORDINATES	GENE

DETD TABLE 5

Inhibition of Human **Fak** mRNA expression in A549 Cells by

FAK 20 mer **Antisense** Oligonucleotides

ISIS #	SEQ ID NO:	GENE TARGET REGION	% mRNA EXPRESSION	% mRNA INHIBITION
control	--	--	100%	0%
15392.	.	.		

DETD TABLE 6

Inhibition of Human **Fak** mRNA expression in A549 Cells by **FAK** 15 mer **antisense** oligonucleotides

ISIS #	SEQ ID NO:	GENE TARGET REGION	% mRNA EXPRESSION	% mRNA INHIBITION
control	--	--	100%	0%
15393.	.	.		

DETD Dose response of **antisense** phosphorothioate oligonucleotide effects on **FAK** levels in A549 cells

DETD TABLE 7

Dose Response of A549 cells to **FAK** Phosphorothioate Oligonucleotides

ISIS #	SEQ ID NO:	ASO Gene Target	Dose	% mRNA Expression	% mRNA Inhibition
control	--	--	--	. .	

DETD . . . as shown in Table 3. The LIPOFECTIN.RTM. to oligonucleotide ratio was maintained at 3 mg/ml LIPOFECTIN.RTM. per 100 nM oligonucleotide. **FAK** protein levels were determined 48 hours after **antisense** treatment in whole cell lysates by anti-**FAK** blotting. Cells on 10cm plates were lysed with 0.5 ml modified RIPA lysis buffer, diluted with 0.5 ml HNTG buffer. . . 150 mM NaCl, 0.1% Triton X-100, 10% glycerol), incubated with agarose beads, and cleared by centrifugation. Immunoprecipitations with a polyclonal **FAK** antibody (Salk Institute of Biological Studies, La Jolla, Calif.; additional **FAK** antibodies available from Upstate Biotechnology Incorporated, Lake Placid, N.Y.) were performed for 4hr at 4.degree. C., collected on protein A. . .

DETD TABLE 8

Dose Response of A549 cells to **FAK** Phosphorothioate Oligonucleotides

ISIS #	SEQ ID NO:	ASO Gene Target	Dose	% protein Expression	% protein Inhibition
control	--	--	--	. .	

DETD Effect of **FAK antisense** phosphorothioate oligonucleotides on growth factor stimulated migration and invasion

DETD Integrin-regulated **focal adhesion kinase** (**FAK**) is an important component of epidermal (EGF) and platelet-drived (PDGF) growth factor-induced motility of primary fibroblasts, smooth muscle, and adenocarcinoma cells. To measure the effect of **FAK antisense** oligonucleotides on cell migration, a modified Boyden chamber (Millipore, Bedford, Mass.) assay was used (Sieg, D. J., et al., J.. . .

DETD TABLE 9

Effect of **FAK Antisense** Phosphorothioate Oligonucleotides

on EGF-Stimulated Cell Migration

ISIS #	SEQ ID NO:	Target	ASO Gene (ng/ml)	EGF A.sub.600
control	--	--	2.5. . .	

DETD **FAK antisense** oligonucleotides were tested in an in vitro invasion assay using an .about.1 mm MATRIGELD (Becton Dickinson, Franklin Lakes, N.J.) basement. . .

DETD TABLE 10

Effect of **FAK Antisense** Phosphorothioate Oligonucleotides on Tumor Cell Invasion

ISIS #	SEQ ID NO:	Target	ASO Gene (.mu.g/chamber)	MATRIGEL .RTM. Migration (A.sub.600)
control	--	.	.	

DETD **FAK antisense** oligonucleotides in a retinal neovascularization model

DETD **FAK antisense** oligonucleotides were tested in a rabbit model of retinal neovascularization (Kimura, H., et al., Invest. Opthalmol. Vis. Sci., 1995, 36,. . .

DETD . . . be detected in the first week and retinal hemorrhaging began by the end of the third week. Animals receiving the **antisense** **FAK** oligonucleotide showed no evidence of retinal neovascularization over a four week period.

DETD . . . <210> SEQ ID NO 3
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **antisense** sequence
- - <400> SEQUENCE: 3
- - ccgcgggctc acagtggtcg - # - # - # 20
- - -. . . <210> SEQ ID NO 4
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **antisense** sequence
- - <400> SEQUENCE: 4
- - ggcgccgtga agcgaaggca - # - # - # 20
- - -. . . <210> SEQ ID NO 5
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **antisense** sequence
- - <400> SEQUENCE: 5
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- - ggtaagcagc tgccattatt - # - #
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- - -. . . <210> SEQ ID NO 11
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- - -. . . <210> SEQ ID NO 13
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- - <400> SEQUENCE: 14
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- - -. . . <210> SEQ ID NO 17
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- - -. . . <210> SEQ ID NO 18
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- - <400> SEQUENCE: 18
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- - -. . . <210> SEQ ID NO 19
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- - -. . . <210> SEQ ID NO 20
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- - -. . . <210> SEQ ID NO 21
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- - -. . . <210> SEQ ID NO 22
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- - <400> SEQUENCE: 22
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- - -. . . <210> SEQ ID NO 23
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<220> FEATURE:
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- - gcgggctcac agtgg - # - #
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- - -. . . <210> SEQ ID NO 24
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- - <400> SEQUENCE: 25
- - gttctgctcg gaccg - # - #
- # 15
- - -. . . <210> SEQ ID NO 26
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- - <400> SEQUENCE: 26
- - aactgcagaa ggcac - # - #
- # 15
- - -. . . <210> SEQ ID NO 27
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- - ctcccttccg ttatt - # - #
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- - -. . . <210> SEQ ID NO 28
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- - agatgctagg tatct - # - #
- # 15
- - -. . . <210> SEQ ID NO 29
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- - ttgctagatg ctagg - # - #
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- - taagcagctg ccatt - # - #
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- - -. . . <210> SEQ ID NO 33
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- - tggcttatct tcagt - # - #
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- - ttagggatgg tgccg - # - #
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- - -. . . <210> SEQ ID NO 35
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- - ttggtttcca atcgg - # - #
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- - tcaaccagat ggtca - # - #
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- - ctgaatatca tgatt - # - #
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- - <400> SEQUENCE: 40
- - tgatgcttaa aagct - # - #
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- - -. . . <210> SEQ ID NO 41
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- - <400> SEQUENCE: 41
- - tgtgaacata aattg - # - #
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- - -. . . <210> SEQ ID NO 42
<211> LENGTH: 15
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<223> OTHER INFORMATION: **antisense** sequence
- - <400> SEQUENCE: 42
- - ggtagtttag gaatt - # - #
- # 15
- - -. . .
CLM What is claimed is:
1. An **antisense** compound 8 to 30 nucleobases in length targeted to nucleobases 1-120 of the 5'-untranslated region, nucleobases 150-230 of the 5'-untranslated region, translational termination region or nucleobases 3424-3679 of the 3'-untranslated region of a nucleic acid molecule encoding human **focal adhesion**

kinase (SEO ID NO: 1), wherein said **antisense** compound inhibits the expression of said **focal adhesion kinase**.

2. The **antisense** compound of claim 1 which is an **antisense** oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide has a sequence comprising SEQ ID NO: 3, 4, 6, 7, 8, 9, 16, 17, 18, 20 or 23.

. . .

4. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

5. The **antisense** compound of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage.

6. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

7. The **antisense** compound of claim 6 wherein the modified sugar moiety is a 2'-O-methoxyethyl moiety.

8. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

9. The **antisense** compound of claim 8 wherein the modified nucleobase is a 5-methyl cytosine.

10. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

11. A composition comprising the **antisense** compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

13. The composition of claim 11 wherein the **antisense** compound is an **antisense** oligonucleotide.

14. A method of inhibiting the expression of human **focal adhesion kinase** in cells or tissues comprising contacting said cells or tissues with the **antisense** in vitro compound of claim 1 so that expression of **focal adhesion kinase** is inhibited.

15. An **antisense** compound up to 30 nucleobases in length targeted to the coding region of a nucleic acid molecule encoding human **focal adhesion kinase**, wherein said **antisense** compound inhibits the expression of said **focal adhesion kinase** and has a sequence comprising at least an 8 nucleobasic portion of SEQ ID NO: 11, 12, 14, 15, 30,. . .

16. The **antisense** compound of claim 15 which is an **antisense** oligonucleotide.

17. The **antisense** compound of claim 16 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

18. The **antisense** compound of claim 17 wherein the modified internucleoside linkage is a phosphorothioate linkage.

19. The **antisense** compound of claim 16 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

20. The **antisense** compound of claim 19 wherein the modified sugar moiety is a 2'-O-methoxyethyl moiety.

21. The **antisense** compound of claim 16 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

22. The **antisense** compound of claim 21 wherein the modified nucleobase is a 5-methyl cytosine.

23. The **antisense** compound of claim 16 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

24. A composition comprising the **antisense** compound of claim 15 and a pharmaceutically acceptable carrier or diluent.

26. The composition of claim 24 wherein the **antisense** compound is an **antisense** oligonucleotide.

27. A method of inhibiting the expression of human **focal adhesion kinase** in cells or tissues comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 15 so that expression of **focal adhesion kinase** is inhibited.

28. A method of inhibiting neovascularization in the eye associated with expression of **focal adhesion kinase** in an animal comprising intravitreally administering to said animal a therapeutically or prophylactically effective amount of the **antisense** compound of claim 3 or 15 targeted to a nucleic acid molecule encoding human **focal adhesion kinase** wherein said **antisense** compound inhibits the expression of human **focal adhesion kinase**.

29. An in vitro method of inhibiting migration of cells associated with expression of **focal adhesion kinase** comprising administering to said cells a therapeutically or prophylactically effective amount of an **antisense** compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human **focal adhesion kinase** comprising SEQ ID NO: 18 wherein said **antisense** compound inhibits the expression of human **focal adhesion kinase**.

L4 ANSWER 6 OF 37 USPATFULL

ACCESSION NUMBER:	2000:127756 USPATFULL			
TITLE:	Diagnostic apparatus utilizing radiation interaction with biological tissue			
INVENTOR(S):	Masychev, Victor, Moscow, Russian Federation			
PATENT ASSIGNEE(S):	Rosslyn Medical Limited, London, United Kingdom (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6123719		20000926	
	WO 9715226		19970501	
APPLICATION INFO.:	US 1998-65031		19980423	(9)
	WO 1996-GB2604		19961024	
			19980423	PCT 371 date
			19980423	PCT 102(e) date

NUMBER	DATE

PRIORITY INFORMATION: GB 1995-21784 19951024
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kamm, William E.
LEGAL REPRESENTATIVE: Biebel & French
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 45 Drawing Figure(s); 27 Drawing Page(s)
LINE COUNT: 1181
DETD . . . in the preliminary measurement of the PNC-signal from the lesion and in subsequent synchronisation of its proliferative activity with e.g. 5-**florouracil** in the course of 3-5 days and in daily registration of the PNC-signals from lesion (Tfi,Tfc,Tfl). When the PNC-signal is. . .

L4 ANSWER 7 OF 37 USPATFULL
ACCESSION NUMBER: 2000:102123 USPATFULL
TITLE: **Antisense** inhibition of PI3K p85 expression
INVENTOR(S): Monia, Brett P., La Costa, CA, United States
Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6100090		20000808	
APPLICATION INFO.:	US 1999-344521		19990625	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 2852
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Antisense** inhibition of PI3K p85 expression
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of PI3K p85. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding PI3K p85. Methods of using these compounds for modulation of PI3K p85 expression and. . .
SUMM The present invention provides compositions and methods for modulating the expression of PI3K p85. In particular, this invention relates to **antisense** compounds, particularly oligonucleotides, specifically hybridizable with nucleic acids encoding human PI3K p85. Such oligonucleotides have been shown to modulate the. . .
SUMM . . . He et al., Blood, 1993, 82, 3530-3538; Kontos et al., Mol. Cell. Biol., 1998, 18, 4131-4140). It also interacts with **focal adhesion kinase** (**FAK**), a cytoplasmic tyrosine kinase involved in integrin signaling and is thought to be a substrate and effector of **FAK**. The p85 subunit also interacts with profilin, an actin binding protein that facilitates actin polymerization (Bhargavi et al., Biochem. Mol.. . .
SUMM Alternatively, **antisense** technology is emerging as an effective means for reducing the expression of specific gene products and may therefore prove to. . .
SUMM The present invention is directed to **antisense** compounds, particularly oligonucleotides, which are targeted to a nucleic acid encoding PI3K p85, and which modulate the expression of PI3K p85. Pharmaceutical and other compositions comprising the **antisense** compounds of the invention are also provided. Further provided are methods of modulating the expression of PI3K p85 in cells or tissues comprising contacting said cells or tissues with one or more of the **antisense** compounds or compositions of the invention. Further

provided are methods of treating an animal, particularly a human, suspected of having. . . associated with expression of PI3K p85 by administering a therapeutically or prophylactically effective amount of one or more of the **antisense** compounds or compositions of the invention.

SUMM The present invention employs oligomeric **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding PI3K p85, ultimately modulating the amount of PI3K p85 produced. This is accomplished by providing **antisense** compounds which specifically hybridize with one or more nucleic acids encoding PI3K p85. As used herein, the terms "target nucleic. . . modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "**antisense**". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with. . .

SUMM It is preferred to target specific nucleic acids for **antisense**. "Targeting" an **antisense** compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins. . . molecule encoding PI3K p85. The targeting process also includes determination of a site or sites within this gene for the **antisense** interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within. . .

SUMM . . . also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM . . . between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an **antisense** compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An **antisense** compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal. . . to cause a loss of utility, and there is a sufficient degree of complementarity to avoid nonspecific binding of the **antisense** compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of. . .

SUMM **Antisense** compounds are commonly used as research reagents and diagnostics. For example, **antisense** oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. **Antisense** compounds are also used, for example, to distinguish between functions of various members of a biological pathway. **Antisense** modulation has, therefore, been harnessed for research use.

SUMM The specificity and sensitivity of **antisense** is also harnessed by those of skill in the art for therapeutic uses. **Antisense** oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. **Antisense** oligonucleotides have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established. . .

SUMM While **antisense** oligonucleotides are a preferred form of **antisense** compound, the present invention comprehends other oligomeric **antisense** compounds, including but not limited to oligonucleotide mimetics such as are described below. The **antisense** compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides). Particularly preferred **antisense** compounds are **antisense** oligonucleotides, even more preferably

those comprising from about 12 to about 25 nucleobases. As is known in the art, a. . .

SUMM Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B. ed., CRC Press, 1993. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes **antisense** compounds which are chimeric compounds. "Chimeric" **antisense** compounds or "chimeras," in the context of this invention, are **antisense** compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit,. . .

SUMM Chimeric **antisense** compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide. . .

SUMM The **antisense** compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase. . .

SUMM The **antisense** compounds of the invention are synthesized in vitro and do not include **antisense** compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of **antisense** molecules. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures. . .

SUMM The **antisense** compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which,. . .

SUMM The **antisense** compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. For therapeutics,. . . having a disease or disorder which can be treated by modulating the expression of PI3K p85 is treated by administering **antisense** compounds in accordance with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an **antisense** compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the **antisense** compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation or tumor. . .

SUMM The **antisense** compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding PI3K p85, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the **antisense** oligonucleotides of the invention with a nucleic acid encoding PI3K p85 can be detected by means known in the art.. . .

SUMM The present invention also includes pharmaceutical compositions and formulations which include the **antisense** compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending. . .

SUMM . . . No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include an **antisense** RNA. U.S. Pat. No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in

liposomes. WO 97/04787 to Love et al. discloses liposomes comprising **antisense** oligonucleotides targeted to the raf gene.

SUMM . . . can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., **Antisense** Res. Dev., 1995, 5, 115-121; Takakura et al., **Antisense** & Nucl. Acid Drug Dev., 1996, 6, 177-183).

SUMM Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more **antisense** compounds and (b) one or more other chemotherapeutic agents which function by a non-**antisense** mechanism. Examples of such chemotherapeutic agents include, but are not limited to, anticancer drugs such as daunorubicin, dactinomycin, doxorubicin, bleomycin, mitomycin, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-fluorouracil (**5-FU**), floxuridine (5-FUdR), methotrexate (MTX), colchicine, vincristine, vinblastine, etoposide, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, The Merck Manual of Diagnosis. . . Manual of Diagnosis and Therapy, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). Other non-**antisense** chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used together or. . .

SUMM In another related embodiment, compositions of the invention may contain one or more **antisense** compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional **antisense** compounds targeted to a second nucleic acid target. Numerous examples of **antisense** compounds are known in the art. Two or more combined compounds may be used together or sequentially.

DETD The effect of **antisense** compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the. . .

DETD Treatment with **Antisense** Compounds:

DETD **Antisense** modulation of PI3K p85 expression can be assayed in a variety of ways known in the art. For example, P13K. . .

DETD . . . dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after **antisense** oligonucleotide treatment of test samples.

DETD Eighteen hours after **antisense** treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL.TM. (TEL-TEST "B" Inc., Friendswood, Tex.).. . .

DETD **Antisense** Inhibition of PI3K p85 Expression-phosphorothioate Oligodeoxynucleotides

DETD **Antisense** Inhibition of PI3K p85 Expression-phosphorothioate 2'-MOE Gapmer Oligonucleotides

DETD . . . <400> SEQUENCE: 7

20 agcc

- <210> SEQ ID NO 8

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: **Antisense** Oligonucleotide

- <400> SEQUENCE: 8

18 tt

- <210> SEQ ID NO 9

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: **Antisense** Oligonucleotide

- <400> SEQUENCE: 9
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- <210> SEQ ID NO 10
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- <400> SEQUENCE: 10
18 ag
- <210> SEQ ID NO 11
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 11
18 tg
- <210> SEQ ID NO 12
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 12
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- <210> SEQ ID NO 13
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- <400> SEQUENCE: 13
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- <210> SEQ ID NO 14
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- <210> SEQ ID NO 15
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- <210> SEQ ID NO 16
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- <210> SEQ ID NO 17
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- <400> SEQUENCE: 17
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- <210> SEQ ID NO 18
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 18
18 tg
- <210> SEQ ID NO 19
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 19
18 gg
- <210> SEQ ID NO 20
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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18 tt
- <210> SEQ ID NO 21
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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- <210> SEQ ID NO 22
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<213> ORGANISM: Artificial Sequence
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- <400> SEQUENCE: 22
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<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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- <400> SEQUENCE: 23
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- <210> SEQ ID NO 24
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<213> ORGANISM: Artificial Sequence
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- <400> SEQUENCE: 24
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- <210> SEQ ID NO 26
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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- <400> SEQUENCE: 26
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- <210> SEQ ID NO 27
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- <400> SEQUENCE: 27
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- <210> SEQ ID NO 28
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- <400> SEQUENCE: 28
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- <210> SEQ ID NO 29
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- <400> SEQUENCE: 29
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- <210> SEQ ID NO 30
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- <400> SEQUENCE: 30
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- <210> SEQ ID NO 31
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<213> ORGANISM: Artificial Sequence
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- <400> SEQUENCE: 31
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- <210> SEQ ID NO 32
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- <400> SEQUENCE: 32
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- <210> SEQ ID NO 33
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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- <400> SEQUENCE: 33
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- <210> SEQ ID NO 34
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<220> FEATURE:
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- <400> SEQUENCE: 34
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- <210> SEQ ID NO 35
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- <400> SEQUENCE: 35
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- <210> SEQ ID NO 36
<211> LENGTH: 18
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- <400> SEQUENCE: 36
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- <210> SEQ ID NO 37
<211> LENGTH: 18
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- <400> SEQUENCE: 37
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- <210> SEQ ID NO 38
<211> LENGTH: 18
<212> TYPE: DNA
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- <400> SEQUENCE: 38
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- <210> SEQ ID NO 39
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
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- <400> SEQUENCE: 39
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- <210> SEQ ID NO 40
<211> LENGTH: 18
<212> TYPE: DNA
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- <400> SEQUENCE: 40
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- <210> SEQ ID NO 41
<211> LENGTH: 18
<212> TYPE: DNA
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- <400> SEQUENCE: 41
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- <210> SEQ ID NO 42
<211> LENGTH: 18
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide

- <400> SEQUENCE: 42
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- <400> SEQUENCE: 43
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- <210> SEQ ID NO 44
<211> LENGTH: 18
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 44
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- <210> SEQ ID NO 45
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 45
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- <210> SEQ ID NO 46
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 46
18 ta
- <210> SEQ ID NO 47
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- <400> SEQUENCE: 47
18 aa

CLM What is claimed is:

1. An **antisense** compound 8 to 30 nucleobases in length targeted to nucleobases 88-3314 of the coding region of human pI3K p85 (SEQ ID NO: 1), wherein said **antisense** compound specifically hybridizes with and inhibits the expression of human pI3K p85.

2. The **antisense** compound of claim 1 which is an **antisense** oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

4. The **antisense** compound of claim 3 wherein the modified internucleoside linkage is a phosphorothioate linkage.

5. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

6. The **antisense** compound of claim 5 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

7. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

8. The **antisense** compound of claim 7 wherein the modified nucleobase is a 5-methylcytosine.

9. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

10. The **antisense** compound of claim 1 which is targeted to a nucleic acid molecule encoding a truncated form of human PI3K p85.

. . .

11. An **antisense** compound up to 30 nucleobases in length comprising at least an 8-nucleobase portion of SEQ ID NO: 21, 22, 27,.

. .

12. The **antisense** compound of claim 11 which is an **antisense** oligonucleotide.

13. The **antisense** compound of claim 12 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

14. The **antisense** compound of claim 13 wherein the modified internucleoside linkage is a phosphorothioate linkage.

15. The **antisense** compound of claim 12 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

16. The **antisense** compound of claim 15 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

17. The **antisense** compound of claim 12 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

18. The **antisense** compound of claim 17 wherein the modified nucleobase is a 5-methylcytosine.

19. The **antisense** compound of claim 12 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

. . . expression of human pI3K p85 in human cells or tissues comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 1 so that expression of human pI3K p85 is inhibited.

. . . expression of human pI3K p85 in human cells or tissues comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 3 so that expression of human pI3K p85 is inhibited.

L4 ANSWER 8 OF 37 USPATFULL

ACCESSION NUMBER:	2000:15652 USPATFULL			
TITLE:	L-.beta.-dioxolane uridine analogs and methods for treating and preventing Epstein-Barr virus infections			
INVENTOR(S):	Chu, Chung K., Athens, GA, United States Qu, Fucheng, Lawrenceville, NJ, United States Cheng, Yung-Chi, Woodbridge, CT, United States			
PATENT ASSIGNEE(S):	Yale University, New Haven, CT, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6022876		20000208	
APPLICATION INFO.:	US 1997-954922		19971021	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-749263, filed on 15 Nov 1996, now patented, Pat. No. US 5792773, issued on 11 Aug 1998
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Crane, L. Eric
LEGAL REPRESENTATIVE: Coleman, Henry D., Sudol, R. Neil
NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1315
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD (2S,4S)-1 -[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-**florouracil** (15) and (2S,4R)-1-[2-(Hydroxymethyl)-1,3-dioxola-4-yl]-5-**florouracil** (16) Data of .beta.-isomer 15: Rf-0.61 (MeOH/CHCl.sub.3, 1:4). UV(H2O): (pH 7) 275.0 nm (.epsilon. 9018), (pH 11) 274.5 nm (.epsilon.7408),. . .

L4 ANSWER 9 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000393792 EMBASE
TITLE: Phase II study of vinorelbine with protracted fluorouracil infusion as a second- or third-line approach for advanced breast cancer patients previously treated with anthracyclines.
AUTHOR: Berruti A.; Sperone P.; Bottini A.; Gorzegno G.; Lorusso V.; Brunelli A.; Botta M.; Tampellini M.; Donadio M.; Mancarella S.; De Lena M.; Alquati P.; Dogliotti L.
CORPORATE SOURCE: Dr. L. Dogliotti, Oncologia Medica, Azienda Ospedaliera San
Luigi, Regione Gonzole 10, 10043 Orbassano, Italy. luigi.dogliotti@unito.it
SOURCE: Journal of Clinical Oncology, (1 Oct 2000) 18/19 (3370-3377).
Refs: 43
ISSN: 0732-183X CODEN: JCONDN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . patients was 15 months; median overall survival of the entire population was 22 months. Conclusion: Vinorelbine associated with protracted infusional **florouracil** is an active and manageable scheme in advanced breast cancer patients previously treated with anthracyclines. The response obtained is durable.. . .

L4 ANSWER 10 OF 37 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001028037 MEDLINE
DOCUMENT NUMBER: 20432544 PubMed ID: 10974385
TITLE: Proliferation parameters in epidermoid carcinomas of the anal canal.
AUTHOR: Wong C S; Tsang R W; Cummings B J; Fyles A W; Couture J; Brierley J D; Pintilie M
CORPORATE SOURCE: Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, 610 University Avenue, Toronro, Ontario M5G 2M9, Canada.
SOURCE: RADIOTHERAPY AND ONCOLOGY, (2000 Sep) 56 (3) 349-53.
Journal code: RAE. ISSN: 0167-8140.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322

Last Updated on STN: 20010322
Entered Medline: 20001116

AB . . . tumor proliferation does not have an apparent adverse impact on outcome in anal carcinomas managed by split-course XRT with concurrent 5-**florouracil** and mitomycin C.

L4 ANSWER 11 OF 37 USPATFULL

ACCESSION NUMBER:	1999:159822 USPATFULL
TITLE:	**Antisense** inhibiton of human G-alpha-12 expression
INVENTOR(S):	Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998206		19991207	
APPLICATION INFO.:	US 1999-256496		19990223	(9)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	LeGuyader, John L.			
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
LINE COUNT:	2921			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Antisense** inhibiton of human G-alpha-12 expression

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of G-alpha-12. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding G-alpha-12. Methods of using these compounds for modulation of G-alpha-12 expression and for treatment. . .

SUMM The present invention provides compositions and methods for modulating the expression of G-alpha-12. In particular, this invention relates to **antisense** compounds, particularly oligonucleotides, specifically hybridizable with nucleic acids encoding human G-alpha-12. Such oligonucleotides have been shown to modulate the expression. . .

SUMM Results from studies in human embryonic kidney cells demonstrated that constitutive activation of G-alpha-12 stimulated RhoA-dependant phosphorylation of p125 **focal adhesion kinase**, paxillin and p130 Crk-associated substrate, all of which have been implicated in the regulation of proliferation and transformation (Needham and. . .

SUMM Finally, studies using both **antisense** vectors expressing a 43 base fragment of mouse G-alpha-12 in **antisense** orientation and constitutively active forms of G-alpha-12 to investigate retinoic acid-stimulated differentiation of P19 mouse embryonal carcinoma cells found that. . .

SUMM . . . or investigating G-alpha-12 function have involved the use of antibodies, mutant forms of the protein which are constitutively active and **antisense** expression vectors.

SUMM . . . therapeutic protocols and consequently there remains a long felt need for additional agents capable of effectively inhibiting G-alpha-12 function. Therefore, **antisense** oligonucleotides may provide a promising new pharmaceutical tool for the effective and specific modulation of G-alpha-12 expression.

SUMM The present invention is directed to **antisense** compounds, particularly oligonucleotides, which are targeted to a nucleic acid encoding G-alpha-12, and which modulate the expression of G-alpha-12. Pharmaceutical and other compositions comprising the **antisense** compounds of the invention are also provided. Further provided are methods of modulating the expression of G-alpha-12 in cells or tissues comprising contacting said cells or tissues with one or more of the

antisense compounds or compositions of the invention. Further provided are methods of treating an animal, particularly a human, suspected of having. . . condition associated with expression of G-alpha-12 by administering a therapeutically or prophylactically effective amount of one or more of the **antisense** compounds or compositions of the invention.

SUMM The present invention employs oligomeric **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding G-alpha-12, ultimately modulating the amount of G-alpha-12 produced. This is accomplished by providing **antisense** compounds which specifically hybridize with one or more nucleic acids encoding G-alpha-12. As used herein, the terms "target nucleic acid". . . modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "**antisense**". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with. . .

SUMM It is preferred to target specific nucleic acids for **antisense**. "Targeting" an **antisense** compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins. . . acid molecule encoding G-alpha-12. The targeting process also includes determination of a site or sites within this gene for the **antisense** interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within. . .

SUMM . . . also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM . . . between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an **antisense** compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An **antisense** compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal. . . to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the **antisense** compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of. . .

SUMM **Antisense** compounds are commonly used as research reagents and diagnostics. For example, **antisense** oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. **Antisense** compounds are also used, for example, to distinguish between functions of various members of a biological pathway. **Antisense** modulation has, therefore, been harnessed for research use.

SUMM The specificity and sensitivity of **antisense** is also harnessed by those of skill in the art for therapeutic uses. **Antisense** oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. **Antisense** oligonucleotides have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established. . .

SUMM While **antisense** oligonucleotides are a preferred form of **antisense** compound, the present invention comprehends other oligomeric **antisense** compounds, including but not limited to oligonucleotide mimetics such as are described below. The **antisense** compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases. Particularly preferred are **antisense** oligonucleotides comprising from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides).

As is. . .

SUMM Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press, 1993. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes **antisense** compounds which are chimeric compounds. "Chimeric" **antisense** compounds or "chimeras," in the context of this invention, are **antisense** compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit,. . .

SUMM Chimeric **antisense** compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide. . .

SUMM The **antisense** compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase. . .

SUMM The **antisense** compounds of the invention are synthesized in vitro and do not include **antisense** compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of **antisense** molecules. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures. . .

SUMM The **antisense** compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which,. . .

SUMM The **antisense** compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. For therapeutics,. . . of having a disease or disorder which can be treated by modulating the expression of G-alpha-12 is treated by administering **antisense** compounds in accordance with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an **antisense** compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the **antisense** compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation or tumor. . .

SUMM The **antisense** compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding G-alpha-12, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the **antisense** oligonucleotides of the invention with a nucleic acid encoding G-alpha-12 can be detected by means known in the art. Such. . .

SUMM The present invention also includes pharmaceutical compositions and formulations which include the **antisense** compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending. . .

SUMM . . . No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include an **antisense** RNA. U.S. Pat. No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in

liposomes. WO 97/04787 to Love et al. discloses liposomes comprising **antisense** oligonucleotides targeted to the raf gene.

SUMM . . . be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4' isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., **Antisense** Res. Dev., 1995, 5, 115-121; Takakura et al., **Antisense** & Nucl. Acid Drug Dev., 1996, 6, 177-183).

SUMM Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more **antisense** compounds and (b) one or more other chemotherapeutic agents which function by a non-**antisense** mechanism. Examples of such chemotherapeutic agents include, but are not limited to, anticancer drugs such as daunorubicin, dactinomycin, doxorubicin, bleomycin, mitomycin, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-fluorouracil (**5-FU**), floxuridine (5-FUdR), methotrexate (MTX), colchicine, vincristine, vinblastine, etoposide, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, The Merck Manual of Diagnosis. . . Manual of Diagnosis and Therapy, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). Other non-**antisense** chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used together or. . .

SUMM In another related embodiment, compositions of the invention may contain one or more **antisense** compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional **antisense** compounds targeted to a second nucleic acid target. Numerous examples of **antisense** compounds are known in the art. Two or more combined compounds may be used together or sequentially.

DETD The effect of **antisense** compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the. . .

DETD Treatment with **Antisense** Compounds:

DETD **Antisense** modulation of G-alpha-12 expression can be assayed in a variety of ways known in the art. For example, G-alpha-12 mRNA. . .

DETD . . . dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after **antisense** oligonucleotide treatment of test samples.

DETD Eighteen hours after **antisense** treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL.TM. (TEL-TEST "B" Inc., Friendswood, Tex.).. . .

DETD **Antisense** Inhibition of G-alpha-12 Expression-Phosphorothioate Oligodeoxynucleotides

DETD **Antisense** Inhibition of G-alpha-12 Expression-Phosphorothioate 2'-MOE Gapmer Oligonucleotides

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CLM What is claimed is:

1. An **antisense** compound 8 to 30 nucleotides in length targeted to a nucleic acid molecule encoding human G-alpha-12, wherein said **antisense** compound inhibits the expression of human G-alpha-12.

2. The **antisense** compound of claim 1 which is an **antisense** oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

4. The **antisense** compound of claim 3 wherein the modified internucleoside linkage is a phosphorothioate linkage.

5. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

6. The **antisense** compound of claim 5 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

7. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

8. The **antisense** compound of claim 7 wherein the modified nucleobase is a 5-methylcytosine.

9. The **antisense** compound of claim 1 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

. . . the expression of human G-alpha-12 in human cells or tissues comprising contacting said cells or tissues in vitro with the **antisense** compound of claim 1 so that expression of human G-alpha-12 is inhibited.

L4 ANSWER 12 OF 37 USPATFULL

ACCESSION NUMBER:	1999:142139 USPATFULL		
TITLE:	**Antisense** modulation of G-alpha-13 expression		
INVENTOR(S):	Cowsert, Lex M., Carlsbad, CA, United States		
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5981732		19991109
APPLICATION INFO.:	US 1998-205860		19981204 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Degen, Nancy		
ASSISTANT EXAMINER:	Epps, Janet		
LEGAL REPRESENTATIVE:	Law Offices of Jane Massey Licata		
NUMBER OF CLAIMS:	24		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2986		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Antisense** modulation of G-alpha-13 expression

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of G-alpha-13. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding G-alpha-13. Methods of using these compounds for modulation of G-alpha-13 expression and for treatment. . .

SUMM The present invention provides compositions and methods for modulating the expression of G-alpha-13. In particular, this invention relates to **antisense** compounds, particularly oligonucleotides, specifically hybridizable with nucleic acids encoding human G-alpha-13. Such oligonucleotides have been shown to modulate the expression. . .

SUMM Results from studies in human embryonic kidney cells demonstrated that constitutive activation of G-alpha-13 stimulated RhoA-dependant phosphorylation of p125 **focal adhesion kinase**, paxillin and p130 Crk-associated substrate, all of which have been implicated in the regulation of proliferation and transformation (Needham and. . .

SUMM Finally, studies using both **antisense** vectors, expressing a 45 base fragment of mouse G-alpha-13 in **antisense** orientation and constitutively active forms of G-alpha-13 to investigate retinoic acid-stimulated differentiation of P19 mouse embyronal carcinoma cells found that. . .

SUMM . . . at inhibiting or investigating G-alpha-13 function have involved the use of mutant forms of the protein which are constitutively active, **antisense** expression vectors and gene knock-outs in mice.

SUMM . . . therapeutic protocols and consequently there remains a long felt need for additional agents capable of effectively inhibiting G-alpha-13 function. Therefore, **antisense** oligonucleotides may provide a promising new pharmaceutical tool for the effective and specific modulation of G-alpha-13 expression.

SUMM The present invention is directed to **antisense** compounds, particularly oligonucleotides, which are targeted to a nucleic acid encoding G-alpha-13, and which modulate the expression of G-alpha-13. Pharmaceutical and other compositions comprising the **antisense**

compounds of the invention are also provided. Further provided are methods of modulating the expression of G-alpha-13 in cells or tissues comprising contacting said cells or tissues with one or more of the **antisense** compounds or compositions of the invention. Further provided are methods of treating an animal, particularly a human, suspected of having. . . condition associated with expression of G-alpha-13 by administering a therapeutically or prophylactically effective amount of one or more of the **antisense** compounds or compositions of the invention.

SUMM The present invention employs oligomeric **antisense** compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding G-alpha-13, ultimately modulating the amount of G-alpha-13 produced. This is accomplished by providing **antisense** compounds which specifically hybridize with one or more nucleic acids encoding G-alpha-13. As used herein, the terms "target nucleic acid". . . modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "**antisense**". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with. . .

SUMM It is preferred to target specific nucleic acids for **antisense** . "Targeting" an **antisense** compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins. . . acid molecule encoding G-alpha-13. The targeting process also includes determination of a site or sites within this gene for the **antisense** interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within. . .

SUMM . . . also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for **antisense** compounds targeted, for example, to DNA or pre-mRNA.

SUMM . . . between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an **antisense** compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An **antisense** compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal. . . to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the **antisense** compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of. . .

SUMM **Antisense** compounds are commonly used as research reagents and diagnostics. For example, **antisense** oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. **Antisense** compounds are also used, for example, to distinguish between functions of various members of a biological pathway. **Antisense** modulation has, therefore, been harnessed for research use.

SUMM The specificity and sensitivity of **antisense** is also harnessed by those of skill in the art for therapeutic uses. **Antisense** oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. **Antisense** oligonucleotides have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established. . .

SUMM While **antisense** oligonucleotides are a preferred form of **antisense** compound, the present invention comprehends other oligomeric **antisense** compounds, including but not limited to oligonucleotide mimetics such as are described below. The **antisense** compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases. Particularly preferred

are **antisense** oligonucleotides comprising from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides).

As is. . .

SUMM Specific examples of preferred **antisense** compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides. . .

SUMM . . . by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, **Antisense** Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press, 1993. Certain of these nucleobases are. . . shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., **Antisense** Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when. . .

SUMM . . . be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes **antisense** compounds which are chimeric compounds. "Chimeric" **antisense** compounds or "chimeras," in the context of this invention, are **antisense** compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit,. . .

SUMM Chimeric **antisense** compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide. . .

SUMM The **antisense** compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase. . .

SUMM The **antisense** compounds of the invention are synthesized in vitro and do not include **antisense** compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of **antisense** molecules. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures. . .

SUMM The **antisense** compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which,. . .

SUMM The **antisense** compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. For therapeutics,. . . of having a disease or disorder which can be treated by modulating the expression of G-alpha-13 is treated by administering **antisense** compounds in accordance with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an **antisense** compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the **antisense** compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation or tumor. . .

SUMM The **antisense** compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding G-alpha-13, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the **antisense** oligonucleotides of the invention with a nucleic acid encoding G-alpha-13 can be detected by means known in the art. Such. . .

SUMM The present invention also includes pharmaceutical compositions and formulations which include the **antisense** compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending. . .

SUMM . . . No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include an

antisense RNA. U.S. Pat. No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in liposomes. WO 97/04787 to Love et al. discloses liposomes comprising **antisense** oligonucleotides targeted to the raf gene.

SUMM . . . can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., **Antisense** Res. Dev., 1995, 5, 115-121; Takakura et al., **Antisense** & Nucl. Acid Drug Dev., 1996, 6, 177-183).

SUMM Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more **antisense** compounds and (b) one or more other chemotherapeutic agents which function by a non-**antisense** mechanism. Examples of such chemotherapeutic agents include, but are not limited to, anticancer drugs such as daunorubicin, dactinomycin, doxorubicin, bleomycin, mitomycin, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-fluorouracil (**5-FU**), floxuridine (5-FUdR), methotrexate (MTX), colchicine, vincristine, vinblastine, etoposide, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, The Merck Manual of Diagnosis. . . Manual of Diagnosis and Therapy, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). Other non-**antisense** chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used together or. . .

SUMM In another related embodiment, compositions of the invention may contain one or more **antisense** compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional **antisense** compounds targeted to a second nucleic acid target. Numerous examples of **antisense** compounds are known in the art. Two or more combined compounds may be used together or sequentially.

DETD The effect of **antisense** compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the. . .

DETD Treatment with **antisense** compounds:

DETD **Antisense** modulation of G-alpha-13 expression can be assayed in a variety of ways known in the art. For example, G-alpha-13 mRNA. . .

DETD . . . dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after **antisense** oligonucleotide treatment of test samples.

DETD Eighteen hours after **antisense** treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL.TM. (TEL-TEST "B" Inc., Friendswood, Tex.).. . .

DETD **Antisense** Inhibition of G-alpha-13 Expression-Phosphorothioate Oligodeoxynucleotides

DETD **Antisense** Inhibition of G-alpha-13 Expression-Phosphorothioate 2'-MOE Gapmer Oligonucleotides

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- - -. . . <210> SEQ ID NO 44
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 44
- - gcccgggtat caaacgac - # - #
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- - -. . . <210> SEQ ID NO 45
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 45
- - ccttgtttcc accattcc - # - #
- # 18
- - -. . . <210> SEQ ID NO 46

<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 46
- - gaaaaccctt gtttccac - # - #
- # 18
- - -. . . <210> SEQ ID NO 47
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 47
- - atattgtaag aaaaccct - # - #
- # 18
- - -. . . <210> SEQ ID NO 48
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 48
- - tcttatagca ggaagata - # - #
- # 18
- - -. . . <210> SEQ ID NO 49
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 49
- - ccgctgtctg cccataat - # - #
- # 18
- - -. . . <210> SEQ ID NO 50
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 50
- - cggtcatagg cattctgt - # - #
- # 18
- - -. . . <210> SEQ ID NO 51
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 51
- - acccagttga aattctcg - # - #
- # 18
- - -. . . <210> SEQ ID NO 52
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 52
- - aatattttac agattcac - # - #
- # 18
- - -. . . <210> SEQ ID NO 53
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<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 53
- - tatccaagtt atccagga - # - #
- # 18
- - -. . . <210> SEQ ID NO 54
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 54
- - tctggttctc caagttta - # - #
- # 18
- - -. . . <210> SEQ ID NO 55
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 55
- - gttgtgatgg aatataat - # - #
- # 18
- - -. . . <210> SEQ ID NO 56
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 56
- - gcaagcagaa tatcttgt - # - #
- # 18
- - -. . . <210> SEQ ID NO 57
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 57
- - tgcctttggt gggtcttc - # - #
- # 18
- - -. . . <210> SEQ ID NO 58
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 58
- - aaagtcgtat tcatggat - # - #
- # 18
- - -. . . <210> SEQ ID NO 59
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 59
- - aagcattttg aaaggaac - # - #
- # 18
- - -. . . <210> SEQ ID NO 60
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 60

- - tctgaccacc tacatcaa - # - #
- # 18
- - -. . . <210> SEQ ID NO 61
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 61
- - gtttcctttc tgatctct - # - #
- # 18
- - -. . . <210> SEQ ID NO 62
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 62
- - tcgaaacatt caaaccaa - # - #
- # 18
- - -. . . <210> SEQ ID NO 63
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 63
- - tattgatgtc acactgtc - # - #
- # 18
- - -. . . <210> SEQ ID NO 64
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 64
- - cacttgagga aacaagga - # - #
- # 18
- - -. . . <210> SEQ ID NO 65
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 65
- - cataagcacc tggtcaaa - # - #
- # 18
- - -. . . <210> SEQ ID NO 66
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 66
- - cgattggtca gtcgatct - # - #
- # 18
- - -. . . <210> SEQ ID NO 67
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 67
- - tgttcagaga ctctgtaa - # - #
- # 18
- - -. . . <210> SEQ ID NO 68

<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 68
- - gctgaaaacc cggttatt - # - #
- # 18
- - -. . . <210> SEQ ID NO 69
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 69
- - agaacagaat tatggaga - # - #
- # 18
- - -. . . <210> SEQ ID NO 70
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 70
- - aagcaagtct gtcttgtt - # - #
- # 18
- - -. . . <210> SEQ ID NO 71
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 71
- - caatttgcac cttctcct - # - #
- # 18
- - -. . . <210> SEQ ID NO 72
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 72
- - gaaatagtct ttgatgct - # - #
- # 18
- - -. . . <210> SEQ ID NO 73
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 73
- - ggatcccctt caaattct - # - #
- # 18
- - -. . . <210> SEQ ID NO 74
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 74
- - cgtttgttcc ggaaacat - # - #
- # 18
- - -. . . <210> SEQ ID NO 75
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 75
- - taagggcttc tgttgctg - # - #
- # 18
- - -. . . <210> SEQ ID NO 76
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 76
- - agtggtgaag tggtggta - # - #
- # 18
- - -. . . <210> SEQ ID NO 77
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
DETD . . . <210> SEQ ID NO 78
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 78
- - tatccttcac gtcgcgga - # - #
- # 18
- - -. . . <210> SEQ ID NO 79
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 79
- - ttgaggttgt catgcaga - # - #
- # 18
- - -. . . <210> SEQ ID NO 80
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 80
- - ttgtacatca ctgtagca - # - #
- # 18
- - -. . . <210> SEQ ID NO 81
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 81
- - aaaagatatt aaaacagc - # - #
- # 18
- - -. . . <210> SEQ ID NO 82
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 82
- - aattctggtt gtaaactg - # - #
- # 18
- - -. . . <210> SEQ ID NO 83

<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 83
- - cgtagaatta agattgtt - # - #
- # 18
- - -. . . <210> SEQ ID NO 84
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 84
- - actaagattt tcaagaag - # - #
- # 18
- - -. . . <210> SEQ ID NO 85
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 85
- - cagctttcag ccacaaac - # - #
- # 18
- - -. . . <210> SEQ ID NO 86
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 86
- - caaatcttgg cgatgagt - # - #
- # 18
- - -. . . <210> SEQ ID NO 87
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: **Antisense** Oligonucleotide
- - <400> SEQUENCE: 87
- - aacagatcaa agcctgca - # - #
- # 18

CLM What is claimed is:

1. An **antisense** compound 8 to 30 nucleobases in length targeted to SEQ ID NO: 1, wherein said **antisense** compound inhibits the expression of human G-alpha-13.

2. The **antisense** compound of claim 1 which is an **antisense** oligonucleotide.

3. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

4. The **antisense** compound of claim 3 wherein the modified internucleoside linkage is a phosphorothioate linkage.

5. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

6. The **antisense** compound of claim 5 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

7. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

8. The **antisense** compound of claim 7 wherein the modified nucleobase is a 5-methylcytosine.

9. The **antisense** compound of claim 2 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

. . . inhibiting expression of G-alpha-13 in human cells or tissues comprising contacting said human cells or tissues in vitro with the **antisense** compound of claim 1 so that expression of human G-alpha-13 is inhibited.

11. An **antisense** compound up to 30 nucleobases in length comprising SEQ ID NO: 9, 13, 14, 15, 16, 17, 18, 19, 20,. . .
12. The **antisense** compound of claim 3 comprising SEQ ID NO: 14, 16, 18, 19, 20, 21, 22, 25, 26, 28, 30, 31,. . .
13. The **antisense** compound of claim 11 which is an **antisense** oligonucleotide.

14. The **antisense** compound of claim 13 wherein the **antisense** oligonucleotide comprises at least one modified internucleoside linkage.

15. The **antisense** compound of claim 14 wherein the modified internucleoside linkage is a phosphorothioate linkage.

16. The **antisense** compound of claim 13 wherein the **antisense** oligonucleotide comprises at least one modified sugar moiety.

17. The **antisense** compound of claim 16 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

18. The **antisense** compound of claim 13 wherein the **antisense** oligonucleotide comprises at least one modified nucleobase.

19. The **antisense** compound of claim 18 wherein the modified nucleobase is a 5-methylcytosine.

20. The **antisense** compound of claim 13 wherein the **antisense** oligonucleotide is a chimeric oligonucleotide.

21. A composition comprising the **antisense** compound of claim 11 and a pharmaceutically acceptable carrier or diluent.

23. The composition of claim 21 wherein the **antisense** compound is an **antisense** oligonucleotide.

. . . inhibiting expression of G-alpha-13 in human cells or tissues comprising contacting said human cells or tissues in vitro with the **antisense** compound of claim 11 so that expression of human G-alpha-13 is inhibited.

L4 ANSWER 13 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95274694 EMBASE
DOCUMENT NUMBER: 1995274694
TITLE: Studies on proliposomes containing 5-**florouracil**.
AUTHOR: Yin C.H.; Liu G.J.; Zhu J.B.
CORPORATE SOURCE: Department of Pharmaceutics, China Pharmaceutical University,Nanjing 210009, China

SOURCE: Proceedings of the Controlled Release Society, (1995) -/22 (482-483).
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
TI Studies on proliposomes containing 5-**florouracil**.

L4 ANSWER 14 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:525636 BIOSIS
DOCUMENT NUMBER: PREV199396139043
TITLE: Effectiveness of combined induction chemotherapy and radiotherapy in advanced nasopharyngeal carcinoma.
AUTHOR(S): Dimery, I. W. (1); Peters, L. J.; Goepfert, H.; Morrison, W. H.; Byers, R. M.; Guillory, C.; McCarthy, K.; Weber, R. S.; Hong, W. K.
CORPORATE SOURCE: (1) Hematol. Oncol. Med. Group Frenso, 7130 N. Millbrook, Suite 100, Fresno, CA 93720 USA
SOURCE: Journal of Clinical Oncology, (1993) Vol. 11, No. 10, pp. 1919-1928.
ISSN: 0732-183X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB. . . overall and progression-free survival in previously untreated patients with stage IV nasopharyngeal carcinoma who received an induction chemotherapy regimen of **florouracil** (5-FU) and cisplatin followed by radiotherapy. Patients and Methods: From January 1985 to January 1990, 47 patients with T1-4N2-3M0 squamous. . .

L4 ANSWER 15 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 93073087 EMBASE
DOCUMENT NUMBER: 1993073087
TITLE: Thyrotropin-secreting pituitary carcinoma.
AUTHOR: Mixson A.J.; Friedman T.C.; Katz D.A.; Feuerstein I.M.; Taubenberger J.K.; Colandrea J.M.; Doppman J.L.; Oldfield E.H.; Weintraub B.D.
CORPORATE SOURCE: NIDDKD, National Institutes of Health, Building 10,Bethesda, MD 20892, United States
SOURCE: Journal of Clinical Endocrinology and Metabolism, (1993) 76/2 (529-533).
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . that the sacral mass was a metastasis from the pituitary tumor. Due to additional metastases in the lung, she received 5-**florouracil**, cytoxan, and adriamycin, with marked decrease in her lesions. Further substantiation of the metastatic pituitary tumor was made when the. . .

L4 ANSWER 16 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92185766 EMBASE
DOCUMENT NUMBER: 1992185766
TITLE: [Enteral nutrition efficacy in patients with esophageal carcinoma receiving combined chemo-radiation therapy].

NUTRIZIONE ENTERALE DURANTE CHEMIO-RADIOTERAPIA NEL CARCINOMA ESOFAGEO.

AUTHOR: Cozzaglio L.; Bozzetti F.; Bidoli P.; Bonfanti G.; Riva L.; Strisciuglio A.

CORPORATE SOURCE: Oncologia Chirurgica 'A', Ist Naz per Studio/Cura dei Tumori, Via G. Venezian, 1,20133 Milano, Italy

SOURCE: Rivista Italiana di Nutrizione Parenterale ed Enterale, (1992) 10/1 (37-42).
ISSN: 0393-5582 CODEN: RINEEK

COUNTRY: Italy

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 011 Otorhinolaryngology
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: Italian

SUMMARY LANGUAGE: English; Italian

AB . . . patients without dysphagia and no nutritional support, group II (NE) patients with dysphagia supported by enteral feeding. Oncological therapies included 5-**florouracil** (1g/m2/day, dl-4) cisplatin (100mg/m2, dl) for two cycles associated with radiotherapy (30 Gy). We have evaluated the feasibility of enteral. . .

L4 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:614666 CAPLUS

DOCUMENT NUMBER: 115:214666

TITLE: Local therapy of malignant brain tumor with 5FU-polymer pellets and histological study of rat brain with implantation of biodegradable CDDP-lactone polymer

AUTHOR(S): Kubo, Osami; Tajika, Yasuhiko; Ara, Tetsuaki; Nitta, Masae; Kumakura, Minoru; Yoshida, Masaru; Imasaka, Minoru; Nagai, Koji

CORPORATE SOURCE: Dep. Neurosurg., Tokyo Women's Med. Coll., Tokyo, Japan

SOURCE: Drug Delivery Syst. (1991), 6(3), 195-200
CODEN: DDSYEI; ISSN: 0913-5006

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Local therapy was carried out by slowly releasing anticancer composite to malignant brain tumors. Either ACNU pellets or 5FU (5-**florouracil**) pellets were administered at the time of the operation or under CT guidance in treating 81 cases of malignant brain tumor. From 1 to 10 pellets contg. 10-20 mg ACNU of from 1-6 pellets contg. 5-20 mg 5FU were administered. In ACNU cases, the response of the tumor tissue to local therapy was not very strong and no peripheral edemas was obsd. on CT. scan. In the 5FU pellets cases, a severe brain edema was seen in and around the pellet from the 7th to 21st days after implantation of pellet. This edema gradually improved and showed low d. only around the lesion. This is presumably due to the occurrence of leucoencephalopathy because of 5FU. Sufficient histol. studies have not yet been carried out. But in one case who was reoperation on the 10th day after pellet implantation, histol. examn. revealed marked tissue necrosis and no remaining tumor cells were seen. Thus the tissue response to 5FU is extremely strong. 5FU-pellet shows a stronger cytotoxic effect and greater degree of tissue infiltration than ACNU. Copolymers of lactic acid and valerolactone with a no.-av. mol. wt. of 1500-2600 were developed as biodegradable carriers for drug delivery. When CDDP-lactone polymer was implanted in the brain of rat, histol., the brain tissue is markedly changed. The area of necrosis and response of connective tissue were seen around the implantation site from 5th day to 20th days.

L4 ANSWER 18 OF 37 LIFESCI COPYRIGHT 2001 CSA

ACCESSION NUMBER: 90:30961 LIFESCI

TITLE: Induction, accumulation, and persistence of sister chromatid exchanges in women with breast cancer receiving cyclophosphamide, adriamycin, and 5-fluorouracil chemotherapy.
AUTHOR: Tucker, J.D.; Wyrobek, A.J.; Ashworth, L.K.; Christensen, M.L.; Burton, G.V.; Carrano, A.V.; Everson, R.B.
CORPORATE SOURCE: Lawrence Livermore Natl. Lab., Biomed. Sci. Div., P.O. Box 5507, L-452, Univ. California, Livermore, CA 94551, USA
SOURCE: CANCER RES., (1990) vol. 50, no. 16, pp. 4951-4956.
DOCUMENT TYPE: Journal
FILE SEGMENT: G; G3; X
LANGUAGE: English
SUMMARY LANGUAGE: English
UT cyclophosphamide; 5-**florouracil**; chemotherapy; carcinoma; sister chromatid exchange; induction; doxorubicin; breast; man

L4 ANSWER 19 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:116642 BIOSIS
DOCUMENT NUMBER: BA91:64032
TITLE: PHASE II TRIAL OF UFT IN ADVANCED COLORECTAL AND GASTRIC CANCER.
AUTHOR(S): MALIK S T A; TALBOT D; CLARKE P I; OSBORNE R; REZNEK R; WRIGLEY P F M; SLEVIN M L
CORPORATE SOURCE: ICRF DEP. MEDICAL ONCOL., HOMERTON HOSPITAL, HOMERTON ROW, LONDON E9 6SR, UK.
SOURCE: BR J CANCER, (1990) 62 (6), 1023-1025.
CODEN: BJCAAI. ISSN: 0007-0920.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB A phase II trial of continuous oral therapy with UFT, a combination of uracil and the 5-**florouracil** analogue 1-(2-tetrahydrofuryl)-5-fluorouracil (Futraful, Ftorafur), was conducted in 40 patients with advanced colorectal cancer and 18 patients with advanced gastric cancer.. . .

L4 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:158830 CAPLUS
DOCUMENT NUMBER: 112:158830
TITLE: 5-Fluorouracil group-containing phospholipids as anticancer agents and preparation thereof
INVENTOR(S): Nakaya, Tadao
PATENT ASSIGNEE(S): Chisso Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01226892	A2	19890911	JP 1988-54330	19880308
JP 06089008	B4	19941109		

OTHER SOURCE(S): MARPAT 112:158830
IT 126192-92-5P 126192-93-6P, Ethyl 3-(5-**florouracil**-1-yl)butyrate 126192-94-7P, 3-(5-Fluorouracil-1-yl)butyric acid 126192-95-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of fluorouracil-contg. of phospholipid anticancer agents)

L4 ANSWER 21 OF 37 USPATFULL
ACCESSION NUMBER: 89:98984 USPATFULL
TITLE: Inhibiting growth of tumors with certain substituted phenoxy dimethyl acids, esters or salts
INVENTOR(S): Numasaki, Yoso, Saitama, Japan

Takahashi, Koichiro, Tokyo, Japan
Ohata, Isao, Saitama, Japan
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4886818		19891212
APPLICATION INFO.:	US 1988-198099		19880524 (7)

DISCLAIMER DATE: 20050719
RELATED APPLN. INFO.: Continuation of Ser. No. US 1986-874547, filed on 16 Jun 1986, now patented, Pat. No. US 4758580

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1985-140901	19850626

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Goldberg, Jerome D.
LEGAL REPRESENTATIVE: Burgess, Ryan & Wayne
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 584
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . 9, 11, 13

and 15 days)
400 oral 73.9 80.4
administration
(1, 3, 5, 7, 9, 11, 13
and 15 days)
5-**Florouracil**
50 oral 17.7 48.7
administration
(1, 3, 5, 7, 9, 11, 13
and 15 days)
100 oral 41.2 74.2
administration
. . .

L4 ANSWER 22 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89190437 EMBASE
DOCUMENT NUMBER: 1989190437
TITLE: Influence of the routes of continuous intrahepatic infusion
of 5-fluorouracil on its pharmacokinetics.
AUTHOR: Didolkar M.S.; Jackson A.J.; Covell D.G.; Walker A.P.; Eddington N.D.
CORPORATE SOURCE: Surgical Oncology Program, University of Maryland Hospital,
Baltimore, MD 21201, United States
SOURCE: Journal of Surgical Oncology, (1989) 41/3 (187-193).
ISSN: 0022-4790 CODEN: JSONAU
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . hepatic artery using newly available mechanical devices is frequently used to treat hepatic metastases to achieve a high concentration of 5-**florouracil** (5-FUra) in the hepatic circulation while minimizing systemic exposure. We compared four routes or
intrahepatic adminstration to find out the., . .

L4 ANSWER 23 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:162287 BIOSIS
DOCUMENT NUMBER: BA87:84388
TITLE: INTERACTION OF DEOXYURIDINE WITH FLUOROURACIL AND DIPYRIDAMOLE IN A HUMAN COLON CANCER CELL LINE.
AUTHOR(S): GREM J L; MULCAHY R T; MILLER E M; ALLEGRA C J; FISCHER P H
CORPORATE SOURCE: INVESTIGATIONAL DRUG BRANCH, CANCER THERAPY EVALUATION PROGRAM, DIV. CANCER TREATMENT, NATL. CANCER INST., EXECUTIVE PLAZA NORTH, ROOM 731, BETHESDA, MD. 20892.
SOURCE: BIOCHEM PHARMACOL, (1989) 38 (1), 51-60.
CODEN: BCPCA6. ISSN: 0006-2952.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB. . . studied. After 4 hr, 25 .mu.M deoxyuridine increased the amount of [3H]FdUMP formed 2- to 4-fold relative to that of **florouracil** .+-. dipyridamole alone. The mechanism by which deoxyuridine increased FdUMP was examined by measuring the distribution of [2-3H]deoxyuridine metabolites following. . .

L4 ANSWER 24 OF 37 USPATFULL
ACCESSION NUMBER: 88:45664 USPATFULL
TITLE: Inhibiting growth of tumors with certain substituted phenoxy dimethyl alkanoic acids, esters or salts
INVENTOR(S): Numasaki, Yoso, Saitama, Japan
Takahashi, Koichiro, Tokyo, Japan
Ohata, Isao, Saitama, Japan
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4758580		19880719
APPLICATION INFO.:	US 1986-874547		19860616 (6)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1985-140901	19850626

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Goldberg, Jerome D.
LEGAL REPRESENTATIVE: Burgess, Ryan & Wayne
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 592
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . 9, 11, 13 and 15 days)
400 oral administration
73.9 80.4
(1, 3, 5, 7, 9, 11, 13 and 15 days)
5-**Florouracil**
50 oral administration
17.7 48.7
(1, 3, 5, 7, 9, 11, 13 and 15 days)
100 oral administration
41.2 74.2
. . .

L4 ANSWER 25 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:313 CAPLUS
DOCUMENT NUMBER: 108:313
TITLE: Antitumor and relevant pharmacological effects of pachyman
AUTHOR(S): Chen, Dingnan; Fan, Yijun; Zhou, Jun; Liang, Zichao
CORPORATE SOURCE: Guangxi Inst. Chin. Mater. Med., Nanning, Peop. Rep.

China
SOURCE: Zhongyao Tongbao (1987), 12(9), 553-5
CODEN: CYTPDT; ISSN: 0254-0029
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB I.p. injection of pachyman, the polysaccharide of Poria cocos, had antitumor effect in mice transplanted with S180 tumor cells but did not potentiate the effect of antitumor agents (5-**florouracil**, cyclophosphamide, etc). At high doses, pachyman inhibited body wt. gain in mice. It promoted the recovery of cyclophosphamide-induced decreases in white blood cells of rats and increased the phagocytic activity of macrophages in mice treated with sheep red cells.

L4 ANSWER 26 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 87053610 EMBASE
DOCUMENT NUMBER: 1987053610
TITLE: Alteration of fluorouracil metabolism in human colon cancer
cells by dipyridamole with a selective increase in fluorodeoxyuridine monophosphate levels.
AUTHOR: Grem J.L.; Fischer P.H.
CORPORATE SOURCE: Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, WI 53792, United States
SOURCE: Cancer Research, (1986) 46/12 I (6191-6199).
CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
030 Pharmacology
LANGUAGE: English
AB . . . block the efflux of FdUrd may provide an effective means of selectively increasing FdUMP levels and enhancing the toxicity of **florouracil**. Furthermore, dipyridamole blocked the efflux of deoxyuridine and prolonged the intracellular half-life of deoxyuridine monophosphate. In cells prelabeled with [2'-3H]dUrd,. . .

L4 ANSWER 27 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1985:263374 BIOSIS
DOCUMENT NUMBER: BA79:43370
TITLE: MANNICH BASE DERIVATIVES OF THROPHYLLINE AND 5 FLUOROURACIL
SYNTHESES PROPERTIES AND TOPICAL DELIVERY CHARACTERISTICS.
AUTHOR(S): SLOAN K B; KOCH S A M; SIVER K G
CORPORATE SOURCE: COLLEGE PHARMACY, UNIV. FLORIDA, GAINESVILLE, FL 32610, USA.
SOURCE: INT J PHARM (AMST), (1984) 21 (3), 251-264.
CODEN: IJPHDE. ISSN: 0378-5173.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Mannich base prodrugs of theophylline and 5-fluorouracil [1,3-bis(4'-morpholinyl)methyl-5-**florouracil**, 7-(dimethylamino)methyltheophylline, 7-(diethylamino)methyltheophylline, 7-(dipropylamino)methyltheophylline, 7-(4'-morpholinyl)methyltheophylline and 7-(pyrrolidyl)methyltheophylline] were prepared and tested for their ability to deliver their parent drugs through hairless. . .

L4 ANSWER 28 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82194995 EMBASE
DOCUMENT NUMBER: 1982194995
TITLE: Combination chemotherapy (vincristine, Adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma.
AUTHOR: Evans A.E.; Land V.J.; Newton W.A.; et al.
CORPORATE SOURCE: Child. Cancer Study Group Oper. Off., Los Angeles, CA

90031, United States
SOURCE: Cancer, (1982) 50/5 (821-826).
CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
007 Pediatrics and Pediatric Surgery
048 Gastroenterology
052 Toxicology
LANGUAGE: English
AB . . . Oncology Group conducted a study of chemotherapy for children with malignant liver tumors. All patients received vincristine, cyclophosphamide, Adriamycin and 5-**florouracil** in 6 weekly cycles for one year. Surgical resection and irradiation were employed when indicated. Between January 1976 and August. . .

L4 ANSWER 29 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1980:225529 BIOSIS
DOCUMENT NUMBER: BA70:18025
TITLE: COMBINED CHEMO THERAPY AND RADIO THERAPY FOR LOCALLY ADVANCED BREAST CANCER.
AUTHOR(S): RUBENS R D; SEXTON S; TONG D; WINTER P J; KNIGHT R K; HAYWARD J L
CORPORATE SOURCE: BREAST UNIT, GUYS HOSP., LONDON SE1 9RT, ENGL., UK.
SOURCE: EUR J CANCER, (1980) 16 (3), 351-356.
CODEN: EJCAAH. ISSN: 0014-2964.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB. . . to receive 4 courses of adriamycin and vincristine (AV) followed by radiotherapy, followed by 8 courses of cyclophosphamide, methotrexate and 5-**florouracil** (CMF) (group A), or radiotherapy followed by 4 courses of AV followed by 8 courses of CMF (group B). The. . .

L4 ANSWER 30 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:140447 CAPLUS
DOCUMENT NUMBER: 92:140447
TITLE: Cell surface alterations associated with exposure of leukemia L1210 cells to fluorouracil
AUTHOR(S): Kessel, David
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Cancer Res. (1980), 40(2), 322-4
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
IT Glycoproteins
RL: FORM (Formation, nonpreparative)
(formation of, in leukmeia L1210, **florouracil** inhibtion of, cell surface alterations in relation to)

L4 ANSWER 31 OF 37 MEDLINE
ACCESSION NUMBER: 81023168 MEDLINE
DOCUMENT NUMBER: 81023168 PubMed ID: 7418311
TITLE: Extravasation of chemotherapeutic agents.
AUTHOR: Blair W F; Kilpatrick W C Jr; Saiki J H; Atler E J
SOURCE: CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1980 Sep) (151) 228-30.
Journal code: DFY; 0075674. ISSN: 0009-921X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198012
ENTRY DATE: Entered STN: 19900316

Last Updated on STN: 19900316
Entered Medline: 19801218

AB . . . an extremity. Other chemotherapeutic agents, singly or in combination, may behave in a similar manner. Our experience with mtomycin and 5-**florouracil** suggests that they will produce a relatively severe ulceration. The efficacy of local measures of treatment after extravasation is not. . .

L4 ANSWER 32 OF 37 MEDLINE
ACCESSION NUMBER: 81023663 MEDLINE
DOCUMENT NUMBER: 81023663 PubMed ID: 7418570
TITLE: Combined treatment of patients with lung carcinoma. (Preliminary results assembled in international cooperative investigation).
AUTHOR: Virsik K; Gavalcova E; Badalik L; Szalmova S; Kandracova Z
SOURCE: CZECHOSLOVAK MEDICINE, (1980) 3 (2) 144-50.
Journal code: D91; 7805372. ISSN: 0139-9179.
PUB. COUNTRY: Czechoslovakia
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198012
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19980206
Entered Medline: 19801216

AB . . . by radical Co60 therapy and 20 patients who in addition to Co60 therapy were given the cytostatic preparation Methotrexate and 5-**Florouracil**. The submitted work is part of an international cooperative study within the framework of the Council of Mutual Economic Assistance. . .

L4 ANSWER 33 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80169847 EMBASE
DOCUMENT NUMBER: 1980169847
TITLE: Morphological study of cleft palate development in 5-fluorouracil-treated hamster fetuses.
AUTHOR: Shah R.M.; Wong D.T.W.
CORPORATE SOURCE: Dept. Oral Biol., Fac. Dent., Univ. British Columbia, Vancouver, Canada
SOURCE: Journal of Embryology and Experimental Morphology, (1980) VOL.57/- (119-128).
CODEN: JEEMAF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
021 Developmental Biology and Teratology
001 Anatomy, Anthropology, Embryology and Histology
030 Pharmacology
016 Cancer
LANGUAGE: English

AB . . . 5-fluorouracil-treated hamster fetuses. The results showed that normal palatal development was completed between days 12 and 13 of gestation. In 5-**florouracil**-assaulted palate the reorientation of shelves from a vertical to horizontal plane was delayed. Crown-rump length, gestational age and fetal weight. . .

L4 ANSWER 34 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1979:109996 CAPLUS
DOCUMENT NUMBER: 90:109996
TITLE: Therapeutic agents for treatment of uterus cancer
INVENTOR(S): Nagai, Tsuneji; Machida, Yoshiharu; Masuda, Hiroshi; Fujiyama, Norimasa; Ito, Susumu; Iwata, Masanori
PATENT ASSIGNEE(S): Teijin Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 53130421	A2	19781114	JP 1977-44149	19770419
JP 56047886	B4	19811112		

AB Sustained-release therapeutic agents for treatment of uterus cancer (for uterine application) comprise hydroxypropyl cellulose [9004-64-2] and polyacrylic acid [9003-01-4] or its salts in addn. to active ingredients such as **florouracil**, cyclophosphamide, mitomycin c, and bleomycin-HCl [67763-87-5]. For example, tablets (2 mm thickness, 13 mm diam.) were prepd. contg. hydroxypropyl cellulose 0.9, polyacrylic acid 1.8, and bleomycin-HCl 300 g. The prepns. can be placed in the cervix uteri.

L4 ANSWER 35 OF 37 MEDLINE
ACCESSION NUMBER: 78045698 MEDLINE
DOCUMENT NUMBER: 78045698 PubMed ID: 924840
TITLE: Neurotoxicosis associated with use of 5-**florouracil**.
AUTHOR: Henness A M; Theilen G H; Madewell B R; Crow S E
SOURCE: JOURNAL OF THE AMERICAN VETERINARY MEDICAL ASSOCIATION, (1977 Oct 15) 171 (8) 692.
Journal code: HAV; 7503067. ISSN: 0003-1488.
PUB. COUNTRY: United States
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197801
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780127
TI Neurotoxicosis associated with use of 5-**florouracil**.

L4 ANSWER 36 OF 37 USPATFULL
ACCESSION NUMBER: 75:68603 USPATFULL
TITLE: Process for producing cyclic-3,5-cytidylic acid by fermentation
INVENTOR(S): Ishiyama, Jiro, Noda, Japan
Yokotsuka, Tamotsu, Nagareyama, Japan
PATENT ASSIGNEE(S): Kikkoman Shoyu Co., Ltd., Noda, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 3926725		19751216	
APPLICATION INFO.:	US 1974-477456		19740607	(5)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1973-U63918	19730608

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Tanenholtz, Alvin E.
LEGAL REPRESENTATIVE: Schuyler, Birch, Swindler, McKie & Beckett
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1157
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Furthermore, strains resistant to chemicals such as 5-**florouracil** and 6-azauracil may also be effectively used in the

present process so far as they have abilities of producing CCMP.

L4 ANSWER 37 OF 37 MEDLINE
ACCESSION NUMBER: 72193871 MEDLINE
DOCUMENT NUMBER: 72193871 PubMed ID: 5063951
TITLE: Therapeutic effects of 5-**florouracil** ointment on various skin diseases.
AUTHOR: Yamamoto K; Sasaki S
SOURCE: GAN NO RINSHO. JAPANESE JOURNAL OF CANCER CLINICS, (1972 Mar) 18 (3) 214-8.
Journal code: KIF; 1257753. ISSN: 0021-4949.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197208
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19720801
TI Therapeutic effects of 5-**florouracil** ointment on various skin diseases.

=> d history

(FILE 'HOME' ENTERED AT 15:28:33 ON 15 DEC 2001)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL' ENTERED AT 15:28:56 ON
15 DEC 2001

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT 15:29:05 ON 15 DEC 2001
L1 6685 S (FOCAL ADHESION KINASE) OR FAK OR PP125FAK
L2 234 S L1 AND (ANTISENS? OR TRIPLEX OR RIBOZYM?)
L3 40 S L2 AND (5()FU) OR FLOROURACIL
L4 37 DUP REM L3 (3 DUPLICATES REMOVED)

=> s l2 and ((5()fu) or florouracil)

L5 8 L2 AND ((5(W) FU) OR FLOROURACIL)

=> d ibib abs tot l5

L5 ANSWER 1 OF 8 USPATFULL
ACCESSION NUMBER: 2001:221154 USPATFULL
TITLE: SH2 domain-containing peptides
INVENTOR(S): Stewart, Timothy A., San Francisco, CA, United States
Lu, Yanmei, Belmont, CA, United States
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States
(U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6326482	B1	20011204	
	WO 9954467		19991028	
APPLICATION INFO.:	US 1999-367206		19990809	(9)
	WO 1999-US8847		19990423	
			19990809	PCT 371 date
			19990809	PCT 102(e) date

	NUMBER	DATE

PRIORITY INFORMATION: US 1998-82767 19980423 (60)
US 1998-11329 19981222 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Davis, Katharine F
LEGAL REPRESENTATIVE: Barnes, Elizabeth M.
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 39 Drawing Figure(s); 29 Drawing Page(s)
LINE COUNT: 4794

AB The present invention relates to nucleotide sequences, including expressed sequence tags (ESTs), oligonucleotide probes, polypeptides, antagonists and agonists vectors and host cells expressing, and immunoadhesions and antibodies to PRO201, PRO308 or PRO309 polypeptides.

The invention further relates to compositions and method for the diagnosis and treatment of neoplasfic cell growth and proliferation in mammals, including humans. The invention is based in part on the identification of genes that are amplified in the genome of tumor cells.

Such gene amplification is expected to be associated with the overexpression of the gene product and contribute to tumorigenesis. Accordingly, the proteins encoded by the amplified genes are believed to

be useful targets for the diagnosis and/or treatment (including prevention) of certain tumors (e.g. cancer) and may act as predictors of

the prognosis of tumor treatment.

L5 ANSWER 2 OF 8 USPATFULL
ACCESSION NUMBER: 2001:188696 USPATFULL
TITLE: **Antisense** modulation of **focal adhesion kinase** expression
INVENTOR(S): Monia, Brett P., La Costa, CA, United States
Gaarde, William A., Carlsbad, CA, United States
Nero, Pamela S., San Diego, CA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001034329	A1	20011025
APPLICATION INFO.:	US 2001-757100	A1	20010109 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US18999, filed on 13 Jul 2000, UNKNOWN Continuation of Ser. No. US 1999-377310, filed on 19 Aug 1999, GRANTED, Pat. No. US 6133031
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kathleen A. Tyrrell, Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
LINE COUNT: 1884
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds, compositions and methods are provided for inhibiting **FAK** mediated signaling. The compositions comprise **antisense** compounds targeted to nucleic acids encoding **FAK**. Methods of using these **antisense** compounds for inhibition of **FAK** expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of **FAK** are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 3 OF 8 USPATFULL
ACCESSION NUMBER: 2001:36655 USPATFULL
TITLE: **Antisense** inhibition of SHP-2 expression
INVENTOR(S): Bennett, C. Frank, Carlsbad, CA, United States
Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6200807	B1	20010313	
APPLICATION INFO.:	US 1999-358683		19990721	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 2592
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of SHP-2. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding SHP-2. Methods of using these compounds for modulation of SHP-2 expression and for treatment of diseases associated with expression of SHP-2 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 8 USPATFULL
ACCESSION NUMBER: 2001:10735 USPATFULL
TITLE: **Antisense** modulation of integrin-linked kinase expression
INVENTOR(S): Bennett, C. Frank, Carlsbad, CA, United States
Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): ISIS Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6177273	B1	20010123	
APPLICATION INFO.:	US 1999-428219		19991026	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Guzo, David
ASSISTANT EXAMINER: McGarry, Sean
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2549
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of Integrin-linked kinase. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding Integrin-linked kinase. Methods of using these compounds for modulation of Integrin-linked kinase expression and for treatment of diseases associated with expression of Integrin-linked kinase are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 8 USPATFULL
ACCESSION NUMBER: 2000:138121 USPATFULL
TITLE: **Antisense** inhibition of **focal**

adhesion kinase expression
INVENTOR(S): Monia, Brett P., LaCosta, CA, United States
Gaarde, William A., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6133031		20001017	
APPLICATION INFO.:	US 1999-377310		19990819	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Lacourciere, Karen A
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 2280
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds, compositions and methods are provided for inhibiting **FAK** mediated signaling. The compositions comprise **antisense** compounds targeted to nucleic acids encoding **FAK**. Methods of using these **antisense** compounds for inhibition of **FAK** expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of **FAK** are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 8 USPATFULL
ACCESSION NUMBER: 2000:102123 USPATFULL
TITLE: **Antisense** inhibition of PI3K p85 expression
INVENTOR(S): Monia, Brett P., La Costa, CA, United States
Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6100090		20000808	
APPLICATION INFO.:	US 1999-344521		19990625	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 2852
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of PI3K p85. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding PI3K p85. Methods of using these compounds for modulation of PI3K p85 expression and for treatment of diseases associated with expression of PI3K p85 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 7 OF 8 USPATFULL
ACCESSION NUMBER: 1999:159822 USPATFULL
TITLE: **Antisense** inhibiton of human G-alpha-12 expression
INVENTOR(S): Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States

(U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998206		19991207	
APPLICATION INFO.:	US 1999-256496		19990223	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: LeGuyader, John L.
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 2921
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of G-alpha-12. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding G-alpha-12. Methods of using these compounds for modulation of G-alpha-12 expression and for treatment of diseases associated with expression of G-alpha-12 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 8 USPATFULL
ACCESSION NUMBER: 1999:142139 USPATFULL
TITLE: **Antisense** modulation of G-alpha-13 expression
INVENTOR(S): Cowsert, Lex M., Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

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